PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 May 2001 (15.05.01)	
International application No. PCT/EP00/08899	**Applicant's or agent's file reference** B703WOORD01
International filing date (day/month/year) 12 September 2000 (12.09.00)	**Priority date** (day/month/year) 14 September 1999 (14.09.99)
Applicant MARTIN, Thomas	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

14 March 2001 (14.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Juan Cruz

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
B703WOORD01		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/08899	12/09/2000	14/09/1999
International Patent Classification (IPC) or national classification and IPC C07D295/205		
Applicant BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/03/2001	17.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Timmermans, M Telephone No. +49 89 2399 8940

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/08899

I. Basis f th report

1. With regard to the **el ments** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-48 as originally filed

Claims, No.:

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-2,9-10.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-2,9-10.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	4-5,8
	No:	Claims	3,6-7
Industrial applicability (IA)	Yes:	Claims	3-8

No: Claims

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The subject-matter of claims 1-2 and 9-10 was not searched. According R.66(1e) PCT, no preliminary examination will be carried out for those claims.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are relevant :

D1: WO 99 40083 A
D2: WO 98 04537 A
D3: WO 96 09297 A
D4: WO 95 32945 A
D5: Rice et al., Current Pharmaceutical Design, 4(5), 1998, p. 381-396

1. The novelty of claims 3-8 of the present application is acknowledged. (Art. 33(2) PCT).

   The compounds which are the object of the present application appear to be new because they differ from the compounds of the prior art at least by the nature of the central building block "M" (phenylene while pyridinyl in D1, 1,5-cyclooctylene in D2 and D4) and/or by the nature of the two propynyl "arms" linked to said central block (amino or amido in D3 and D5).

2. Claims 3 and 6-7 of the present application are considered as lacking an inventive step (Art. 33(3) PCT).

2.1 Document D3, which is considered to represent the most relevant state of the art, discloses tryptase inhibitors such as the compounds of Table 4 (p.389) from which the compounds of claim 3 differs in that they contain propynyl groups linked to a central phenylene block instead of amido substituants.

The problem to be solved by the present invention may therefore be regarded as the provision of alternative phenylene derivatives being tryptase inhibitors.

In view of the structural differences existing between the compounds of the prior art and those of the present application, it is considered that it was not obvious that the modified compounds would retain the desired tryptase inhibiting properties and, in theory, an inventive step could thus be acknowledged.

2.2 However, it must be reminded that the breadth of the claims should be such that it represents a reasonable generalisation over the examples provided, and such that every compound falling within its scope actually provides a solution to the problem underlying the invention. Present claim 3 encompasses compounds (i.e. wherein A1 to A4 are bonds, B1 to B12 are bonds, A5 and A6 are carbonyl, K1 and K2 are amino groups) which lack most of the chemical features of the examplified products (see examples p. 31-32). No inventive step can thus be acknowledged for such compounds.
The same consideration applies for claims 6 and 7 (especially in view of the fact that all examples are symmetrical products).

2.3 Claims 4-5 and 8 are considered to meet the requirements of the PCT regarding inventive step.

3. The industrial applicability of claims 3-8 of the present application is acknowledged (Art. 33(4) PCT).

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH
Patentabteilung
Byk-Gulden-Strasse 2
78467 Konstanz
ALLEMAGNE

Date of mailing (day/month/year) 30 October 2000 (30.10.00)	
Applicant's or agent's file reference B703WOORD01	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/08899	International filing date (day/month/year) 12 September 2000 (12.09.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 14 September 1999 (14.09.99)
Applicant BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
14 Sept 1999 (14.09.99) ✓	99118233.8 ✓	EP	12 Octo 2000 (12.10.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Peggy Steunenberg

Telephone No. (41-22) 338.83.38

So: LDV
Ben SR✓

WO 01/19809
PCT/EP00/08899

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH
Patentabteilung
Byk-Gulden-Strasse 2
78467 Konstanz
ALLEMAGNE

EINGANG
RECEIVED
02. April 2001
Gewerblicher Rechtsschutz

Date of mailing (day/month/year) 22 March 2001 (22.03.01)	
Applicant's or agent's file reference B703WOORD01	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP00/08899	12 September 2000 (12.09.00)	14 September 1999 (14.09.99)

Applicant
BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,BA,BG,BR,CA,CN,CZ,EA,EE,EP,GE,HR,HU,ID,IL,IN,JP,LT,LV,MK,MX,NO,NZ,PL,RO,SG, SI,SK,TR,UA,VN,YU,ZA,ZW

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   22 March 2001 (22.03.01) under No. WO 01/19809

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Form PCT/IB/308 (July 1996)

3897232

RW: PCT/EP00/08899

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH
Patentabteilung
Byk-Gulden-Strasse 2
78467 Konstanz
ALLEMAGNE

Date of mailing (day/month/year)	
15 May 2001 (15.05.01)	
Applicant's or agent's file reference B703WOORD01	**IMPORTANT INFORMATION**

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP00/08899	12 September 2000 (12.09.00)	14 September 1999 (14.09.99)

Applicant
BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,CA,CN,CZ,IL,JP,KR,NO,NZ,PL,RO,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   National :AE,AL,BA,BR,EE,GE,HR,HU,ID,IN,LT,LV,MK,MX,SG,SI,TR,UA,VN,YU,ZA,
   ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
Juan Cruz

Telephone No. (41-22) 338.83.38

B703WOORD01

PCT REQUEST

Original (for SUBMISSION) - printed on 11.09.2000 11:25:05 AM

0 0-1	For receiving Office use only International Application N .	PCT/EP 0 0 / 0 8 8 9 9
0-2	International Filing Date	1 2. 09. 00 1 2 SEP 2000
0-3	Name of receiving Office and "PCT International Application"	EUROPEAN PATENT OFFICE PCT INTERNATIONAL APPLICATION
0-4 0-4-1	Form - PCT/RO/101 PCT Request Prepared using	PCT-EASY Version 2.91 (updated 01.07.2000)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	B703WOORD01
I	Title of Invention	TRYPTASE INHIBITORS
II II-1 II-2 II-4 II-5 II-6 II-7 II-8 II-9 II-10	Applicant This person is: Applicant for Name Address: State of nationality State of residence Telephone No. Facsimile No. e-mail	 applicant only all designated States except US BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH Patentabteilung Byk-Gulden-Straße 2 D-78467 Konstanz Germany DE DE 07531-845226 07531-845321 robert.wild@byk.de
III-1 III-1-1 III-1-2 III-1-4 III-1-5 III-1-6 III-1-7	Applicant and/or Inventor This person is: Applicant for Name (LAST, First) Address: State of nationality State of residence	 applicant and inventor US only MARTIN, Thomas St.-Martins-Weg 13 D-78462 Konstanz Germany DE DE

III-2	Applicant and/or inventor	
III-2-1	This person is:	inventor only
III-2-3	Inventor for	EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE); AE AL AU BA BG BR CN CZ EE GE HR HU ID IL IN JP KR LT LV MK MX NO NZ PL RO SG SI SK TR UA VN YU ZA ZW
III-2-4	Name (LAST, First)	BÄR, Thomas
III-2-5	Address:	Berggässle 5 D-78479 Reichenau Germany
III-3	Applicant and/or inventor	
III-3-1	This person is:	inventor only
III-3-3	Inventor for	EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE); AE AL AU BA BG BR CN CZ EE GE HR HU ID IL IN JP KR LT LV MK MX NO NZ PL RO SG SI SK TR UA VN YU ZA ZW
III-3-4	Name (LAST, First)	STADLWIESER, Josef
III-3-5	Address:	Im Apfelgarten 3 D-78465 Konstanz Germany
III-4	Applicant and/or inventor	
III-4-1	This person is:	inventor only
III-4-3	Inventor for	EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE); AE AL AU BA BG BR CN CZ EE GE HR HU ID IL IN JP KR LT LV MK MX NO NZ PL RO SG SI SK TR UA VN YU ZA ZW
III-4-4	Name (LAST, First)	ULRICH, Wolf-Rüdiger
III-4-5	Address:	Hebelstraße 3 D-78464 Konstanz Germany
III-5	Applicant and/or inventor	
III-5-1	This person is:	inventor only
III-5-3	Inventor for	EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE); AE AL AU BA BG BR CN CZ EE GE HR HU ID IL IN JP KR LT LV MK MX NO NZ PL RO SG SI SK TR UA VN YU ZA ZW
III-5-4	Name (LAST, First)	DOMINIK, Andreas
III-5-5	Address:	Engelbert-Weltin-Weg 1 D-78476 Allenbach Germany

III-6	Applicant and/or inventor	
III-6-1	This person is:	inventor only
III-6-3	Inventor for	EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE); AE AL AU BA BG BR CN CZ EE GE HR HU ID IL IN JP KR LT LV MK MX NO NZ PL RO SG SI SK TR UA VN YU ZA ZW
III-6-4	Name (LAST, First)	BUNDSCHUH, Daniela
III-6-5	Address:	Rheingutstraße 17 D-78462 Konstanz Germany
III-7	Applicant and/or inventor	
III-7-1	This person is:	inventor only
III-7-3	Inventor for	EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE); AE AL AU BA BG BR CN CZ EE GE HR HU ID IL IN JP KR LT LV MK MX NO NZ PL RO SG SI SK TR UA VN YU ZA ZW
III-7-4	Name (LAST, First)	ZECH, Karl
III-7-5	Address:	Am Guckenbühl 17 D-78465 Konstanz Germany
III-8	Applicant and/or inventor	
III-8-1	This person is:	inventor only
III-8-3	Inventor for	EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE); AE AL AU BA BG BR CN CZ EE GE HR HU ID IL IN JP KR LT LV MK MX NO NZ PL RO SG SI SK TR UA VN YU ZA ZW
III-8-4	Name (LAST, First)	SOMMERHOFF, Christian
III-8-5	Address:	Thomaßstraße 7 D-81929 München Germany

PCT REQUEST

Original (for SUBMISSION) - printed on 11.09.2000 11:25:05 AM

IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	common representative
IV-1-1	Name	BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH
IV-1-2	Address:	Patentabteilung Byk-Gulden-Straße 2 D-78467 Konstanz Germany
IV-1-3	Telephone No.	07531-845226
IV-1-4	Facsimile No.	07531-845321
IV-1-5	e-mail	robert.wild@byk.de
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AL AU BA BG BR CA CN CZ EE GE HR HU ID IL IN JP KR LT LV MK MX NO NZ PL RO SG SI SK TR UA US VN YU ZA ZW
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	**Exclusion(s) from precautionary designations**	NONE
VI-1	**Priority claim of earlier regional application**	
VI-1-1	Filing date	14 September 1999 (14.09.1999)
VI-1-2	Number	99118233.8
VI-1-3	Regional Office	EP
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

PCT REQUEST

B703WOORD01

Original (for SUBMISSION) - printed on 11.09.2000 11:25:05 AM

VII-2	**Request to use results of earlier search; reference t that search**		
VII-2-1	Date	13 January 2000 (13.01.2000)	
VII-2-2	Number	99118233.8	
VII-2-3	Country (or regional Office)	EP	
VIII	Check list	number of sheets	electronic file(s) attached
VIII-1	Request	5	-
VIII-2	Description	48	-
VIII-3	Claims	10	-
VIII-4	Abstract	1	b703woord01_version_09001_abstract.txt
VIII-5	Drawings	0	-
VIII-7	TOTAL	64	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-12	Priority document(s)	Item(s) VI-1	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	**Figure of the drawings which should accompany the abstract**		
VIII-19	**Language of filing of the international application**	English	
IX-1	**Signature of applicant or agent**		
IX-1-1	Name	BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH	
IX-1-2	Name of signatory	i.V.Dr.Ulrich Wolf i.V.Dr.Robert Wild	
IX-2	**Signature of applicant or agent**		
IX-2-1	Name (LAST, First)	MARTIN, Thomas	

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	12. 09. 2000	12 SEP 2000
10-2	**Drawings:**		
10-2-1	Received		
10-2-2	Not received		
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**		
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**		
10-5	**International Searching Authority**	ISA/EP	
10-6	**Transmittal of search copy delayed until search fee is paid**		

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
B703WOORD01		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 08899	12/09/2000	14/09/1999
Applicant		
BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has be n furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within on month from th date of mailing of this international search report, submit comments to this Authority.

6. Th figur of th **drawings** to be published with th abstract is Figure No. –

[ ] as sugg sted by th applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figur better characterizes the invention.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,9,10 (all in part)

Present claims 1,2,9 and 10 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds disclosed in claims 3- 8 and in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/08899

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D295/205 C07D295/215 C07C271/20 C07C235/10 C07C237/20
C07D307/42 C07D333/16 A61K31/495 A61K31/16 A61K31/381
A61K31/341 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 40083 A (MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSCHAFTEN) 12 August 1999 (1999-08-12) claims; examples	1,9,10
A	WO 98 04537 A (ARRIS PHARMACEUTICAL CORPORATION) 5 February 1998 (1998-02-05) cited in the application claims; examples	1,9,10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2000	14/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Zervas, B

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RICE ET AL: "Inhibitors of Tryptase for the treatment of Mast Cell-Mediated Diseases" CURRENT PHARMACEUTICAL DESIGN,NL,BENTHAM SCIENCE PUBLISHERS, SCHIPHOL, vol. 4, no. 5, 1998, pages 381-396, XP002108322 ISSN: 1381-6128 page 386, column 390 ---	1,9,10
A	WO 96 09297 A (ARRIS PHARMACEUTICAL CORPORATION) 28 March 1996 (1996-03-28) cited in the application claims; examples ---	1,9,10
A	WO 95 32945 A (ARRIS PHARMACEUTICAL) 7 December 1995 (1995-12-07) cited in the application claims; examples -----	1,9,10

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatl. Application No
PCT/EP 00/08899

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9940083 A	12-08-1999	DE 19851299 A	12-08-1999
		AU 2723099 A	23-08-1999
		AU 2924699 A	23-08-1999
		DE 19851300 A	16-12-1999
		WO 9940073 A	12-08-1999
WO 9804537 A	05-02-1998	AU 3967097 A	20-02-1998
		CN 1226892 A	25-08-1999
		CZ 9900297 A	16-06-1999
		EP 0934293 A	11-08-1999
		FI 990171 A	23-03-1999
		LT 99019 A,B	26-07-1999
		LV 12458 A	20-04-2000
		LV 12459 A	20-04-2000
		LV 12291 A,B	20-06-1999
		NO 990433 A	25-03-1999
		PL 331465 A	19-07-1999
		SI 9720047 A	31-08-1999
		SK 8599 A	13-03-2000
WO 9609297 A	28-03-1996	AU 694275 B	16-07-1998
		AU 3718095 A	09-04-1996
		CA 2200561 A	28-03-1996
		CN 1160398 A	24-09-1997
		CZ 9700870 A	12-11-1997
		EP 0782571 A	09-07-1997
		FI 971171 A	20-03-1997
		HR 950499 A	31-08-1997
		HU 77770 A	28-08-1998
		JP 10506390 T	23-06-1998
		LT 97065 A,B	25-08-1997
		LV 11865 A	20-10-1997
		LV 11865 B	20-01-1998
		NO 971305 A	06-05-1997
		NZ 294392 A	28-05-1999
		PL 319587 A	18-08-1997
		SI 9520101 A	31-12-1997
		SK 37997 A	02-12-1998
		US 6022969 A	08-02-2000
		ZA 9508028 A	18-04-1996
WO 9532945 A	07-12-1995	AT 189211 T	15-02-2000
		AU 2764495 A	21-12-1995
		DE 69514798 D	02-03-2000
		EP 0763016 A	19-03-1997
		JP 10501238 T	03-02-1998
		US 5656660 A	12-08-1997

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19809 A1

(51) International Patent Classification[7]: C07D 295/205, 295/215, C07C 271/20, 235/10, 237/20, C07D 307/42, 333/16, A61K 31/495, 31/16, 31/381, 31/341, A61P 11/00

(21) International Application Number: PCT/EP00/08899

(22) International Filing Date:
12 September 2000 (12.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99118233.8 14 September 1999 (14.09.1999) EP

(71) Applicant *(for all designated States except US)*: **BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH** [DE/DE]; Patentabteilung, Byk-Gulden-Strasse 2, 78467 Konstanz (DE).

(72) Inventors *(for all designated States except CA, US)*: **BÄR, Thomas**; Berggässle 5, 78479 Reichenau (DE). **STADLWIESER, Josef**; Im Apfelgarten 3, 78465 Konstanz (DE). **ULRICH, Wolf-Rüdiger**; Hebelstrasse 3, 78464 Konstanz (DE). **DOMINIK, Andreas**; Engelbert-Weltin-Weg 1, 78476 Allenbach (DE). **BUNDSCHUH, Daniela**; Rheingutstrasse 17, 78462 Konstanz (DE). **ZECH, Karl**; Am Guckenbühl 17, 78465 Konstanz (DE). **SOMMERHOFF, Christian**; Thomassstrasse 7, 81929 München (DE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **MARTIN, Thomas** [DE/DE]; St.-Martins-Weg 13, 78462 Konstanz (DE).

(74) Common Representative: **BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH**; Patentabteilung, Byk-Gulden-Strasse 2, 78467 Konstanz (DE).

(81) Designated States *(national)*: AE, AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/19809 A1

(54) Title: TRYPTASE INHIBITORS

(57) Abstract: Compounds of formula (I), in which M, B1, B2, B3, B4, B5, B6, A1, A2, A3, A4, A5, A6, K1 and K2 have the meanings as indicated in the description are novel effective tryptase inhibitors.

Tryptase inhibitors

Fi ld of application of the invention

The invention relates to novel tryptase inhibitors which are used in the pharmaceutical industry for preparing medicaments.

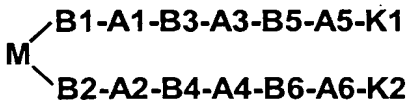
Known technical background

The international applications WO95/32945, WO96/09297, WO98/04537, WO99/40073, WO99/40083, WO99/12918, WO99/24395 and WO99/24407 describe low-molecular-weight compounds for use as tryptase inhibitors.

Description of the invention

It has now been found that the compounds of the formula I, which are described in more detail below, have surprising and particularly advantageous properties.

The invention provides compounds of the formula I

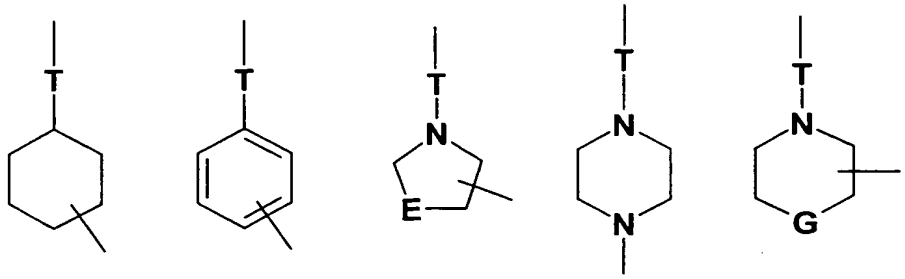


(I)

in which

A1 and A2 are identical or different and are -C(O)-, -NH-, -O- (oxygen), -S- (sulfur), $-S(O)_2-$, $-S(O)_2-NH-$, $-NH-S(O)_2-$, -C(O)-NH-, -NH-C(O)-, -O-C(O)-, -C(O)-O- or a bond,

A3 and A4 are identical or different and are -C(O)-, -O-, -S-, -NH-, -O-C(O)-, -C(O)-O-, -C(O)-NH-, -NH-C(O)- or a bond, or are selected from the group consisting of



where

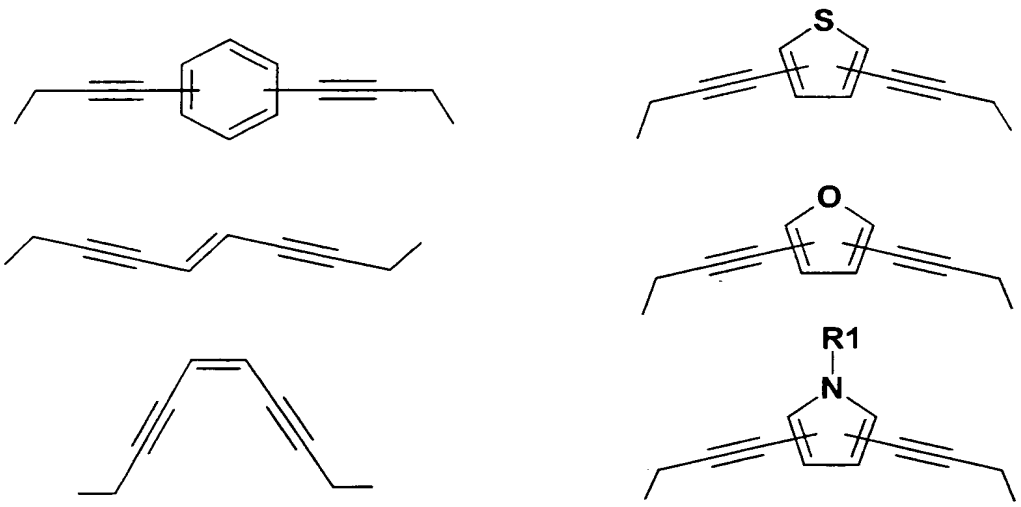
E is -O- (oxygen), -S- (sulfur) or -CH_2- (methylene),

G is -O- (oxygen) or -CH_2- (methylene), and

T is the group -C(O)- or a bond,

A5 and A6 are identical or different and are -C(O)-, -NH-, -O-, -S-, -C(O)-NH-, -NH-C(O)-, -O-C(O)-, -C(O)-O-, -NH-C(O)-NH- or a bond,

M is a central building block selected from the group below



where

R1 is hydrogen, 1-4C-alkyl or 1-4C-alkylcarbonyl,

K1 is -B7-$(C(O))_m$-B9-X1, -B7-$(C(O))_m$-B9-Y1 or -B7-$(C(O))_m$-B9-Z1-B11-X1,

K2 is -B8-$(C(O))_p$-B10-X2, -B8-$(C(O))_p$-B10-Y2 or -B8-$(C(O))_p$-B10-Z2-B12-X2,

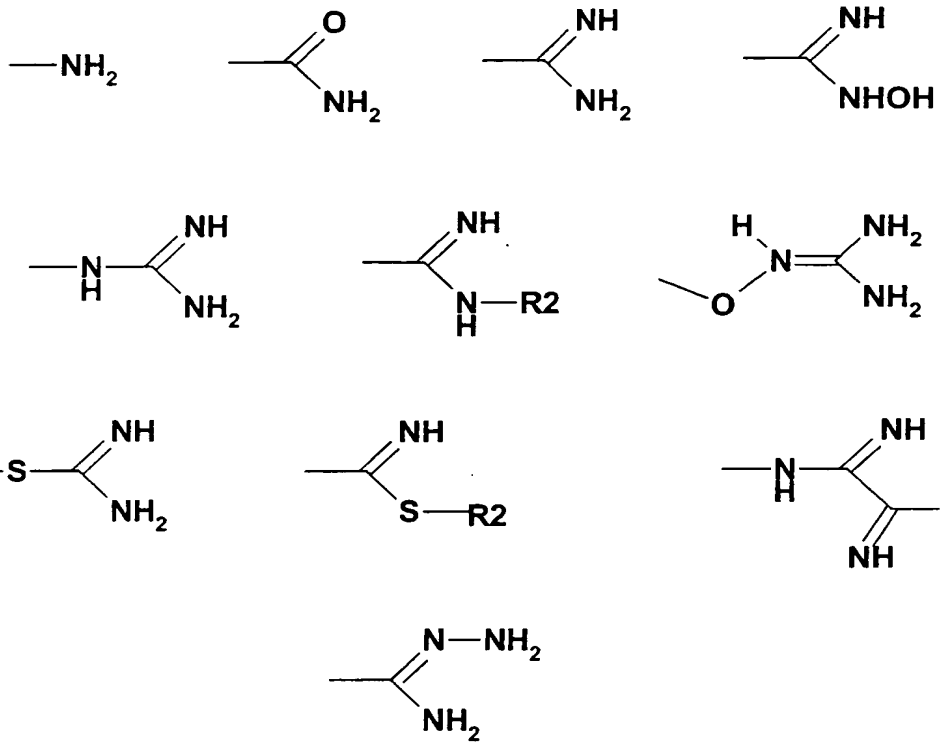
B1, B2, B3, B4, B5 and B6 are identical or different and are a bond or 1-4C-alkylene,

B7, B8, B9, B10, B11 and B12 are identical or different and are a bond or 1-4C-alkylene,

m is 0 or 1,

p is 0 or 1,

X1 and X2 are identical or different and are selected from the group consisting of



where

R2 is 1-4C-alkyl,

Y1 and Y2 are identical or different and are a 4-11C-heteroaryl or 2-7C-heterocycloalkyl radical containing at least one ring nitrogen,

Z1 and Z2 are identical or different and are 5-12C-arylene, 5-12C-heteroarylene, 3-8C-cycloalkylene or 3-8C-heterocycloalkylene,

where each arylene, heteroarylene, cycloalkylene, heterocycloalkylene, heteroaryl or heterocycloalkyl may additionally for its part be substituted by one, two or three substituents selected from the group consisting of hydroxyl, halogen, nitro, cyano, amino, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, carboxyl or aminocarbonyl,

and where on the direct route between the terminal nitrogen atoms 20 to 40, preferably 25 to 40, bonds have to be present,

the salts of these compounds, and the N-oxides of the nitrogen-containing heteroaryls, heterocycloalkyls, heteroarylenes and heterocycloalkylenes, and their salts, where all those compounds are excluded in which one or more of the variables B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, B11 or B12 may assume the meaning of a bond resulting in the direct linkage of two heteroatoms or two carbonyl groups.

1-4C-Alkyl represents straight-chain or branched alkyl radicals having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and the methyl radicals.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

1-4C-Alkoxycarbonyl represents a carbonyl group to which is attached one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxycarbonyl [CH_3O-C(O)-] and the ethoxycarbonyl [CH_3CH_2O-C(O)-] radicals.

1-4C-Alkylcarbonyl represents a radical which, in addition to the carbonyl group, contains one of the abovementioned 1-4C-alkyl radicals. An example which may be mentioned is the acetyl radical.

1-4C-Alkylcarbonyloxy represents a carbonyloxy group to which is attached one of the abovementioned 1-4C-alkyl radicals. An example which may be mentioned is the acetoxy [$CH_3C(O)$-O-] radical.

For the purpose of the invention, halogen is bromine, chlorine and fluorine.

1-4C-Alkylene represents straight-chain or branched 1-4C-alkylene radicals, for example the methylene (-CH_2-), ethylene (-CH_2-CH_2-), trimethylene (-CH_2-CH_2-CH_2-), tetramethylene (-CH_2-CH_2-CH_2-CH_2-), 1,2-dimethylethylene [-$CH(CH_3)$-$CH(CH_3)$-], 1,1-dimethylethylene [-$C(CH_3)_2$-CH_2-], 2,2-dimethylethylene [-CH_2-$C(CH_3)_2$-], isopropylidene [-$C(CH_3)_2$-] or the 1-methylethylene [-$CH(CH_3)$-CH_2-] radicals.

If m is 0, the group -$(C(O))_m$- is a bond.

If p is 0, the group -$(C(O))_p$- is a bond.

4-11C-Heteroaryl represents a - if desired substituted - mono- or bicyclic aromatic hydrocarbon which contains 4 to 11 C atoms and at least one ring nitrogen atom; in addition, one or more of the carbon atoms may be replaced by ring heteroatoms selected from the group consisting of O, N and S. In the case of bicycles, at least one of the rings is aromatic. Examples which may be mentioned are pyrid-4-yl, pyrid-3-yl, pyrimidin-5-yl, imidazol-1-yl and benzimidazol-5-yl.

2-7C-Heterocycloalkyl represents a - if desired substituted - monocyclic saturated or partially saturated hydrocarbon which contains 2 to 7 C atoms and at least one ring nitrogen atom; in addition, one or more carbon atoms may be replaced by ring heteroatoms selected from the group consisting of O, N and S. Examples which may be mentioned are piperid-4-yl, piperazin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl and morpholin-2-yl.

5-12C-Arylene represents a - if desired substituted - divalent mono- or bicyclic aromatic hydrocarbon radical having 5 to 12 C atoms, where in the case of bicyclic aromatic hydrocarbon radicals at least one of the rings is aromatic. The free valencies can both be located at the aromatic, both at the nonaromatic or one at the aromatic and one at the nonaromatic ring. Examples which may be mentioned are 1,4-phenylene, 1,3-phenylene, 1,4-naphthylene and 2,6-naphthylene.

5-12C-Heteroarylene represents an arylene radical as defined above in which 1 to 4 C atoms are replaced by heteroatoms selected from the group consisting of O, N and S. Examples which may be mentioned are 2,5-furylene, 2,5-pyrrolylene, 4,2-pyridylene, 5,2-pyridylene, 2,5-indolylene, 2,6-indolylene, 3,5-indolylene, 3,6-indolylene, 3,5-indazolylene, 3,6-indazolylene, 2,5-benzofuranylene, 2,6-quinolinylene and 4,2-thiazolylene.

3-8C-Cycloalkylene represents a - if desired substituted - divalent monocyclic saturated or partially saturated hydrocarbon radical having 3 to 8 C atoms. Examples which may be mentioned are the 1,3-cyclopentylene, the 1,3-cyclohexylene and preferably the 1,4-cyclohexylene radicals.

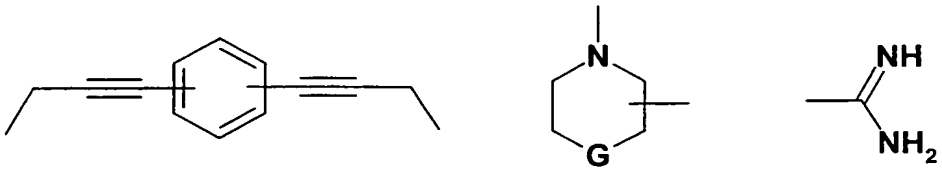
3-8C-Heterocycloalkylene represents a cycloalkylene radical as defined above in which 1 to 3 C atoms are replaced by heteroatoms selected from the group consisting of O, N and S. Examples which may be mentioned are the 1,4-piperidinylene, 1,4-piperazinylene, 2,5-pyrrolidinylene, 4,2-imidazolidinylene and preferably the 4,1-piperidinylene radicals.

Preferred meanings of the groups X1 and X2 are amino, aminocarbonyl, amidino and guanidino.

The particularly preferred meaning of the groups X1 and X2 is amino.

By definition, the groups Z1 and Z2 are located between the groups B9 and B11 (-B9-Z1-B11-) and B10 and B12 (-B10-Z2-B12-), respectively. Accordingly, in the divalent groupings mentioned by way of example (for example 2,6-indolylene), the first number indicates the point of attachment to the group B9 and B10, respectively, and the second number indicates the point of attachment to the group B11 and B12, respectively.

The definitions of M, A3, A4, X1 and X2 contain chemical formulae, such as, for example,



Here, bonds which are unattached on one side mean that the building block is attached at this site to the remainder of the molecule. Bonds which are unattached on both sides mean that this building block has a plurality of sites via which the building block can be attached to the remainder of the molecule.

In the context of this application, the term "terminal nitrogen atom" means in each case a nitrogen atom in the groups designated X1, X2, Y1 and Y2.

If the group X1 or X2 contains only one nitrogen atom, this nitrogen atom is the terminal nitrogen atom.

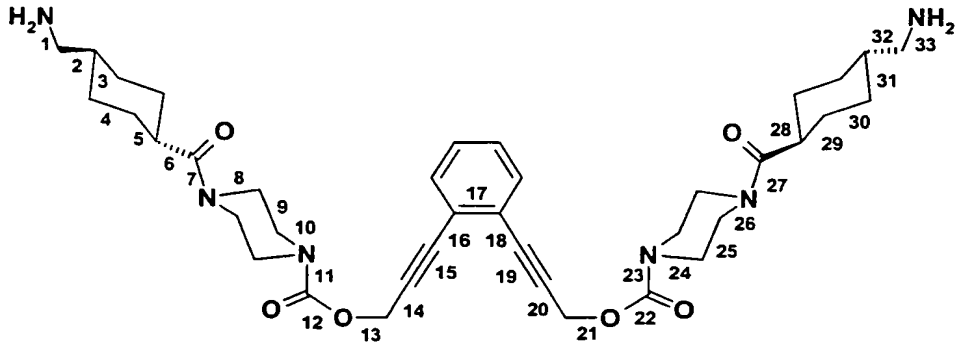
If the group X1 or X2 contains a plurality of nitrogen atoms, the nitrogen atom which is furthest from the atom by means of which the bond to the group B9 (B11) or B10 (B12) is established is the terminal nitrogen atom.

If the group Y1 or Y2 contains only one ring nitrogen atom, this ring nitrogen atom is the terminal nitrogen atom.

If the group Y1 or Y2 contains a plurality of ring nitrogen atoms, the ring nitrogen atom which is furthest from the atom by means of which the bond to the group B9 or B10 is established is the terminal nitrogen atom.

According to the invention, the direct route between the nitrogen atoms which act as terminal nitrogen atoms in the groups defined as X1 (Y1) or X2 (Y2) is considered to be the number of bonds which is obtained by counting the bonds which represent the shortest possible connection between the terminal nitrogen atoms.

The following example is meant to illustrate the determination of the number of bonds on the direct route between two terminal nitrogen atoms:



Here, the direct route comprises 33 bonds.

Suitable salts for compounds of the formula I - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically acceptable salts of inorganic and organic acids customarily used in pharmacy. Those suitable are, on the one hand, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, where the acids are employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are also suitable. Examples of salts with bases which may be mentioned are alkali metal (lithium, sodium, potassium) or calcium, aluminum, magnesium, titanium, ammonium, meglumine or guanidinium salts, where here too the bases are employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

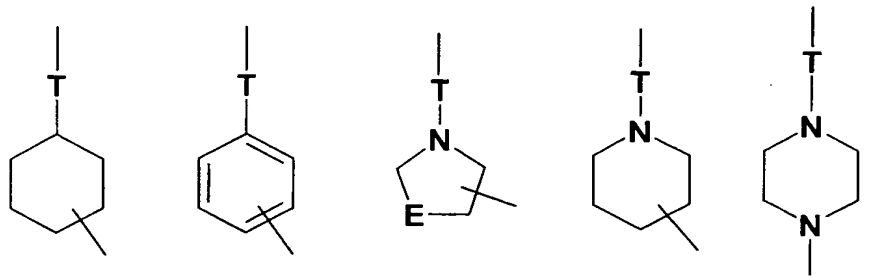
Pharmacologically unacceptable salts which can be obtained initially as process products, for example in the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically acceptable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to the invention, and also their salts, may contain varying amounts of solvents, for example when they are isolated in crystalline form. The invention therefore also embraces all solvates and in particular all hydrates of the compounds of the formula I, and also all solvates and in particular all hydrates of the salts of the compounds of the formula I.

Compounds of the formula I to be emphasized are those in which

A1 and A2 are identical or different and are -C(O)-, -NH-, -O-, -C(O)-NH-, -NH-C(O)-, -O-C(O)-, -C(O)-O- or a bond,

A3 and A4 are identical or different and are -C(O)-, -O-, -NH-, -O-C(O)-, -C(O)-O-, -C(O)-NH-, -NH-C(O)- or a bond, or are selected from the group consisting of



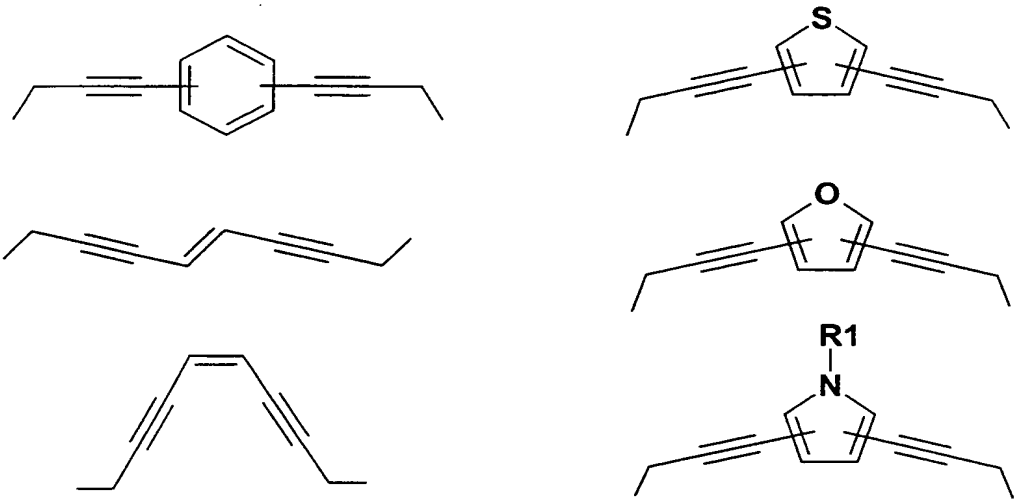
where

E is -O- (oxygen), -S- (sulfur) or -CH_2- (methylene) and

T is the group -C(O)- or a bond,

A5 and A6 are identical or different and are -C(O)-, -NH-, -O-, -C(O)-NH-, -NH-C(O)-, -O-C(O)-, -C(O)-O-, -NH-C(O)-NH- or a bond,

M is a central building block selected from the group below



where

R1 is hydrogen, 1-4C-alkyl or 1-4C-alkylcarbonyl,

K1 is -B7-$(C(O))_m$-B9-X1, -B7-$(C(O))_m$-B9-Y1 or -B7-$(C(O))_m$-B9-Z1-B11-X1,

K2 is -B8-$(C(O))_p$-B10-X2, -B8-$(C(O))_p$-B10-Y2 or -B8-$(C(O))_p$-B10-Z2-B12-X2,

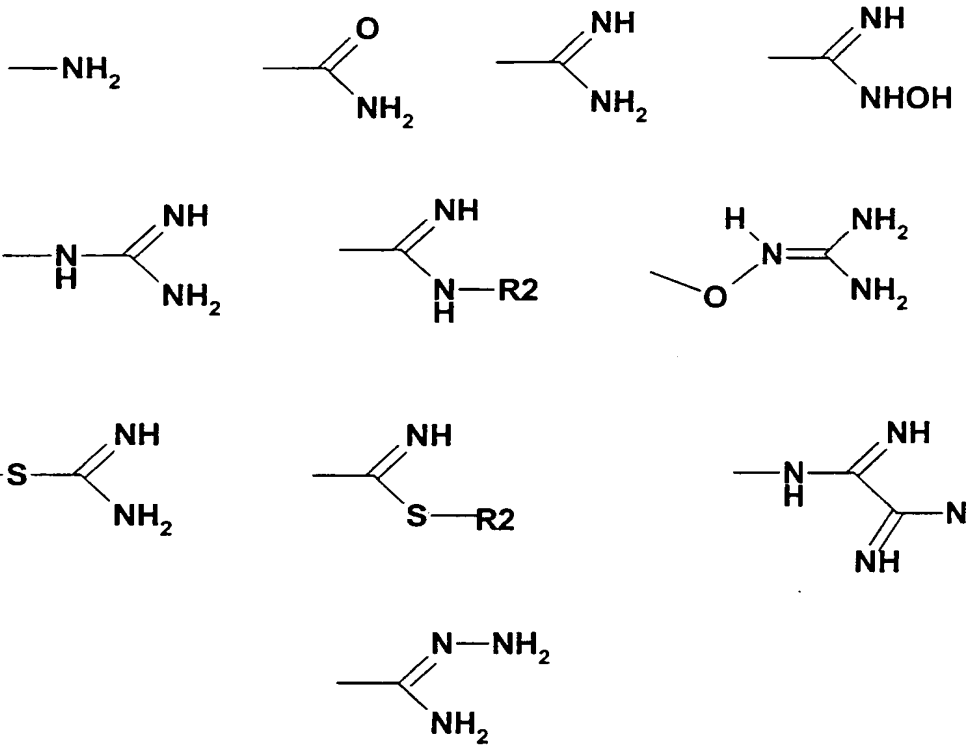
B1, B2, B3, B4, B5 and B6 are identical or different and are a bond or 1-4C-alkylene,

B7, B8, B9, B10, B11 and B12 are identical or different and are a bond or 1-4C-alkylene,

m is 0 or 1,

p is 0 or 1,

X1 and X2 are identical or different and are selected from the group consisting of



where

R2 is 1-4C-alkyl,

Y1 and Y2 are identical or different and are piperid-4-yl, piperid-3-yl, piperazin-1-yl, piperazin-2-yl, morpholin-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, 2-imidazolin-3-yl, 2-imidazolin-2-yl, imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, pyrid-4-yl, pyrid-3-yl, pyridazin-4-yl, pyrimidin-5-yl, pyrimidin-4-yl, indol-3-yl, benzimidazol-4-yl or benzimidazol-5-yl,

Z1 and Z2 are identical or different and are 1,4-phenylene, 1,3-phenylene, 1,4-naphthylene, 2,6-naphthylene, 1,4-cyclohexylene, 1,3-cyclohexylene, 1,3-cyclopentylene, 1,4-piperazinylene, 4,1-piperidinylene, 1,4-piperidinylene, 2,5-pyrrolidinylene, 4,2-imidazolidinylene, 2,5-furylene, 2,5-pyrrolylene, 4,2-pyridylene, 5,2-pyridylene, 2,5-indolylene, 2,6-indolylene, 3,5-indolylene, 3,6-indolylene, 3,5-indazolylene, 3,6-indazolylene, 2,6-quinolinylene, 2,5-benzofuranylene or 4,2-thiazolylene,

where each arylene, heteroarylene, cycloalkylene, heterocycloalkylene, heteroaryl or heterocycloalkyl may additionally for its part be substituted by one, two or three substituents selected from the group consisting of hydroxyl, halogen, nitro, cyano, amino, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, carboxyl or aminocarbonyl,

and where on the direct route between the terminal nitrogen atoms 20 to 40, preferably 25 to 40, bonds have to be present,

the salts of these compounds, and the N-oxides of the nitrogen-containing heteroaryls, heterocycloalkyls, heteroarylenes and heterocycloalkylenes, and their salts, where all those compounds are

excluded in which one or more of the variables B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, B11 or B12 may assume the meaning of a bond, resulting in the direct linkage of two heteroatoms or carbonyl groups.

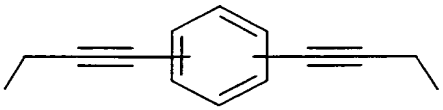
Compounds of the formula I which are to be particularly emphasized are those in which

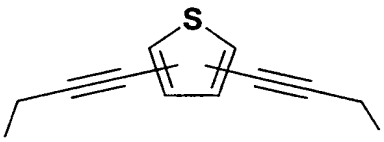
A1 and A2 are identical or different and are -O-, -C(O)-, -O-C(O)-, -NH-C(O)- or a bond,

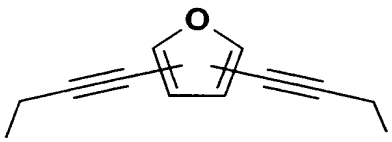
A3 and A4 are identical or different and are 1,4-piperazinylene, 1,4-piperidinylene, 1,4-cyclohexylene, 1,3-phenylene or a bond,

A5 and A6 are identical or different and are -C(O)-, -C(O)-NH-, -NH-C(O)- or -NH-C(O)-NH-,

M is a central building block selected from the group below







K1 is -B7-$(C(O))_m$-B9-Y1 or -B7-$(C(O))_m$-B9-Z1-B11-X1,

K2 is -B8-$(C(O))_p$-B10-Y2 or -B8-$(C(O))_p$-B10-Z2-B12-X2,

B1 and B2 are identical or different and are a bond or methylene,

B3, B4, B5 and B6 are identical or different and are a bond or 1-3C-alkylene,

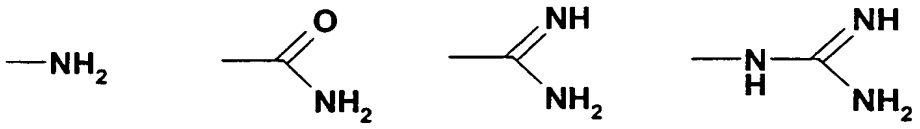
B7, B8, B9 and B10 are identical or different and are a bond or 1-4C-alkylene,

B11 and B12 are identical or different and are a bond or methylene,

m is 0,

p is 0,

X1 and X2 are identical or different and are selected from the group consisting of



Y1 and Y2 are imidazol-1-yl,

Z1 and Z2 are identical or different and are 5,2-pyridinylene, 6-methyl-5,2-pyridinylene, 4,1-piperidinylene, 3,6-indazolylene, 3,6-indolylene, 1,3-phenylene, 1,4-phenylene, 1,3-cyclohexylene or 1,4-cyclohexylene,

and where on the direct route between the terminal nitrogen atoms 20 to 40, preferably 25 to 40, bonds have to be present,

the salts of these compounds, and the N-oxides of nitrogen-containing heteroaryls, heteroarylenes and heterocycloalkylenes, and their salts, where all those compounds are excluded in which one or more of the variables B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, B11 or B12 may assume the meaning of a bond, resulting in the direct linkage of two heteroatoms or carbonyl groups.

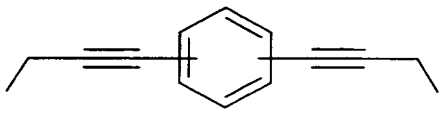
Preferred compounds of the formula I are those in which

A1 and A2 are identical or different and are -O-, -C(O)-, -O-C(O)-, -NH-C(O)- or a bond,

A3 and A4 are identical or different and are 1,4-piperazinylene, 1,4-piperidinylene, 1,4-cyclohexylene, 1,3-phenylene or a bond,

A5 and A6 are identical or different and are -C(O)-, -C(O)-NH-, -NH-C(O)- or -NH-C(O)-NH-,

M is a central building block selected from the group below



K1 is -B7-$(C(O))_m$-B9-Y1 or -B7-$(C(O))_m$-B9-Z1-B11-X1,

K2 is -B8-$(C(O))_p$-B10-Y2 or -B8-$(C(O))_p$-B10-Z2-B12-X2,

B1 and B2 are identical or different and are a bond or methylene,

B3, B4, B5 and B6 are identical or different and are a bond or 1-3C-alkylene,

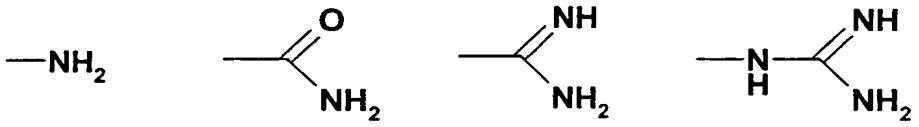
B7, B8, B9 and B10 are identical or different and are a bond or 1-4C-alkylene,

B11 and B12 are identical or different and are a bond or methylene,

m is 0,

p is 0,

X1 and X2 are identical or different and are selected from the groups below



Y1 and Y2 are imidazol-1-yl,

Z1 and Z2 are identical or different and are 5,2-pyridinylene, 6-methyl-5,2-pyridinylene, 4,1-piperidinylene, 3,6-indazolylene, 3,6-indolylene, 1,3-phenylene, 1,4-phenylene, 1,3-cyclohexylene or 1,4-cyclohexylene,

and where on the direct route between the terminal nitrogen atoms 20 to 40, preferably 25 to 40, bonds have to be present,

the salts of these compounds, and also the N-oxides of the nitrogen-containing heteroaryls, heteroarylenes and heterocycloalkylenes, and their salts, where all those compounds are excluded in which one or more of the variables B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, B11 or B12 may assume the meaning of a bond, resulting in the direct linkage of two heteroatoms or carbonyl groups.

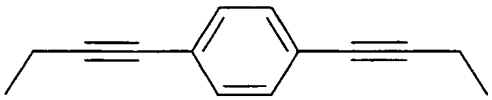
Particularly preferred compounds of the formula I are those in which

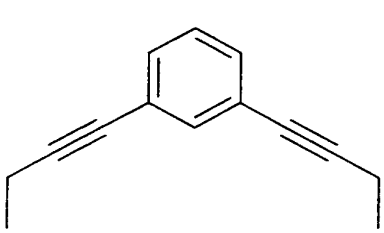
A1 and A2 are -O-C(O)-,

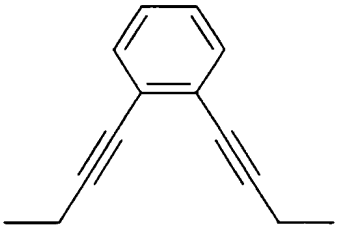
A3 and A4 are 1,4-piperazinylene,

A5 and A6 are identical or different and are -C(O)- or -C(O)-NH-,

M is a central building block selected from the groups below







K1 is -B7-$(C(O))_m$-B9-Z1-B11-X1,

K2 is -B8-$(C(O))_p$-B10-Z2-B12-X2,

B1, B2, B3, B4, B5 and B6 are a bond,

B7 and B8 are identical or different and are a bond or methylene,

B9 and B10 are a bond,

B11 and B12 are methylene,

m is 0,

p is 0,

X1 and X2 are amino,

Z1 and Z2 are identical or different and are 1,4-phenylene or 1,4-cyclohexylene,

and the salts of these compounds.

Further particularly preferred compounds of the formula I are

1,2-bis[4-(trans-4-aminomethylcyclohexylcarbonyl)-1-piperazinylcarbonyl-1-oxyprop-2-ynyl]benzene;

1,4-bis[4-(trans-4-aminomethylcyclohexylcarbonyl)-1-piperazinylcarbonyl-1-oxyprop-2-ynyl]benzene;

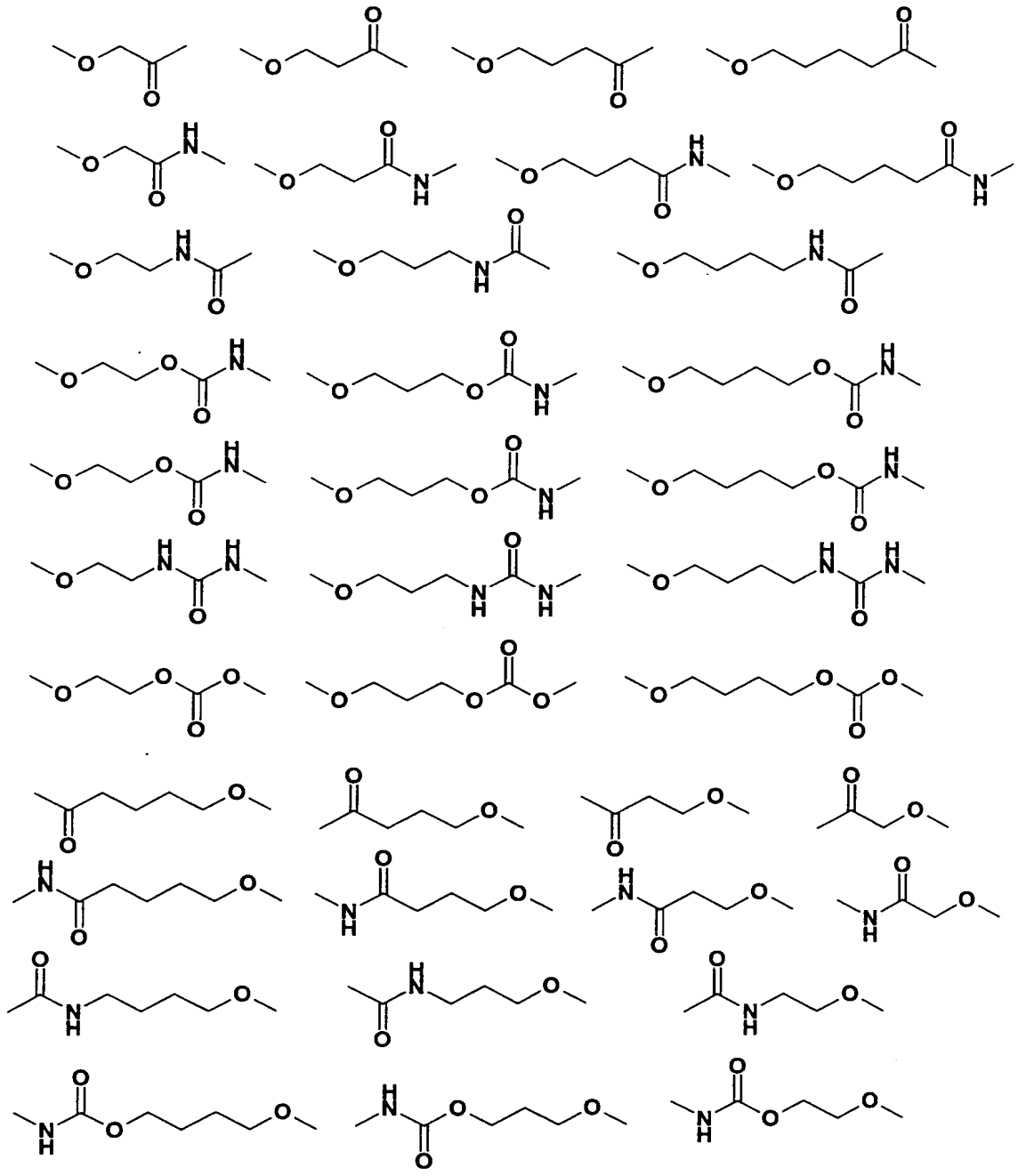
1,2-bis[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyprop-2-ynyl]benzene;

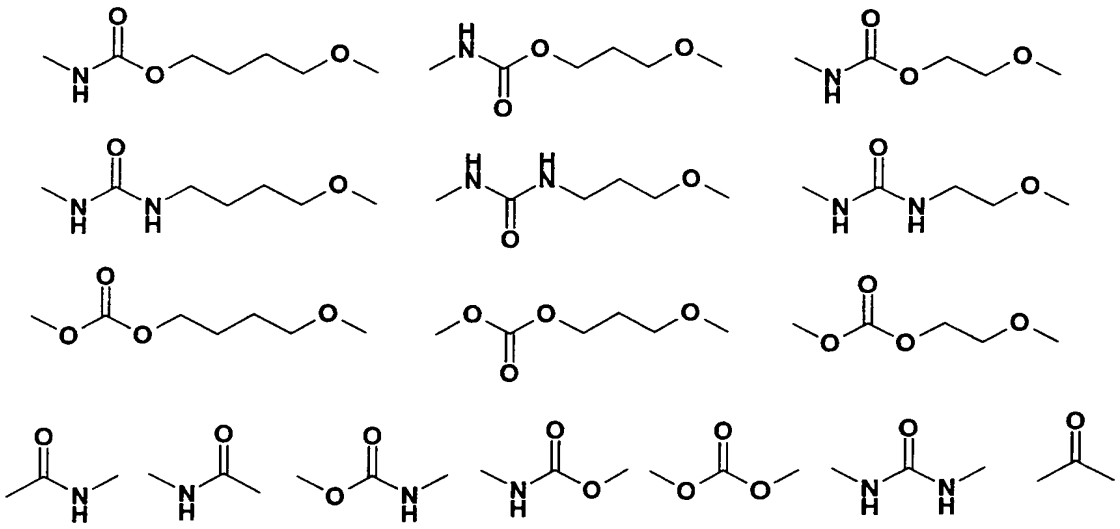
1,3-bis[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyprop-2-ynyl]benzene;

and the salts of these compounds.

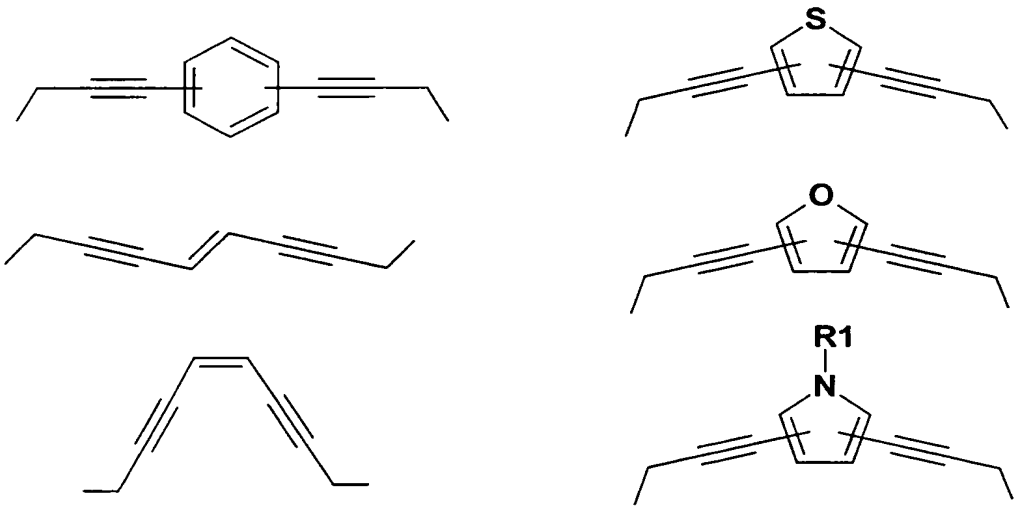
An embodiment (embodiment a) of the compounds of the formula I are those in which

-B1-A1-B3-A3-B5-A5- and -B2-A2-B4-A4-B6-A6- are identical or different and are selected from the groups below





M is a central building block selected from the groups below



where

R1 is hydrogen, 1-4C-alkyl or 1-4C-alkylcarbonyl,

K1 is -B7-$(C(O))_m$-B9-X1, -B7-$(C(O))_m$-B9-Y1 or -B7-$(C(O))_m$-B9-Z1-B11-X1,

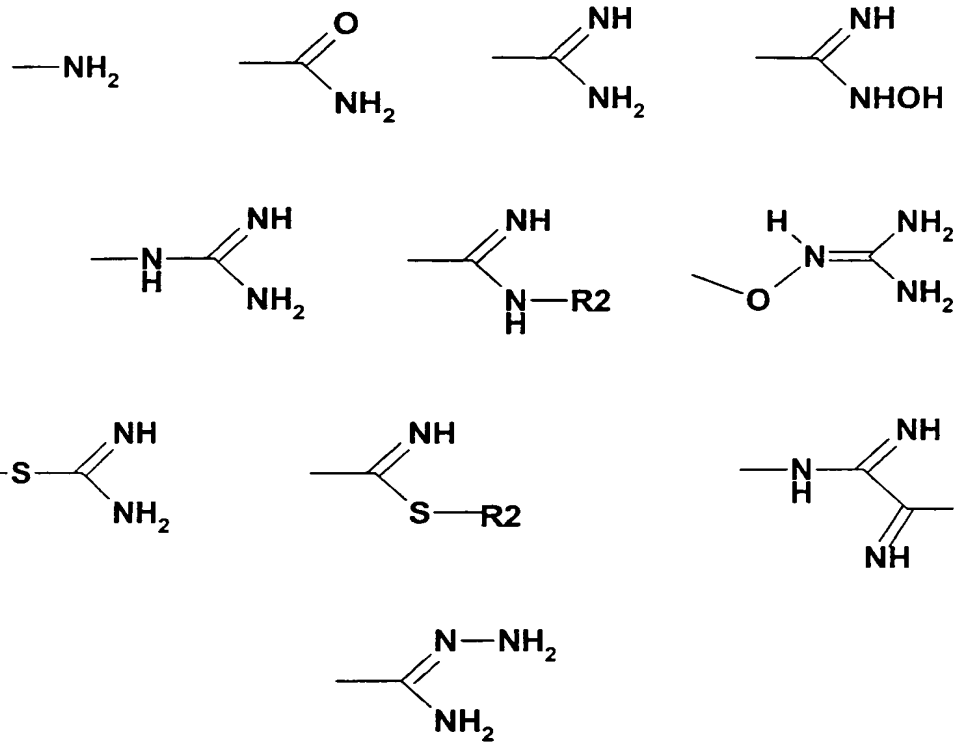
K2 is -B8-$(C(O))_p$-B10-X2, -B8-$(C(O))_p$-B10-Y2 or -B8-$(C(O))_p$-B10-Z2-B12-X2,

B7, B8, B9, B10, B11 and B12 are identical or different and are a bond or 1-4C-alkylene,

m is 0 or 1,

p is 0 or 1,

X1 and X2 are identical or different and are selected from the groups below



where

R2 is 1-4C-alkyl,

Y1 and Y2 are identical or different and are piperid-4-yl, piperid-3-yl, piperazin-1-yl, piperazin-2-yl, morpholin-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, 2-imidazolin-3-yl, 2-imidazolin-2-yl, imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, pyrid-4-yl, pyrid-3-yl, pyridazin-4-yl, pyrimidin-5-yl, pyrimidin-4-yl, indol-3-yl, benzimidazol-4-yl or benzimidazol-5-yl,

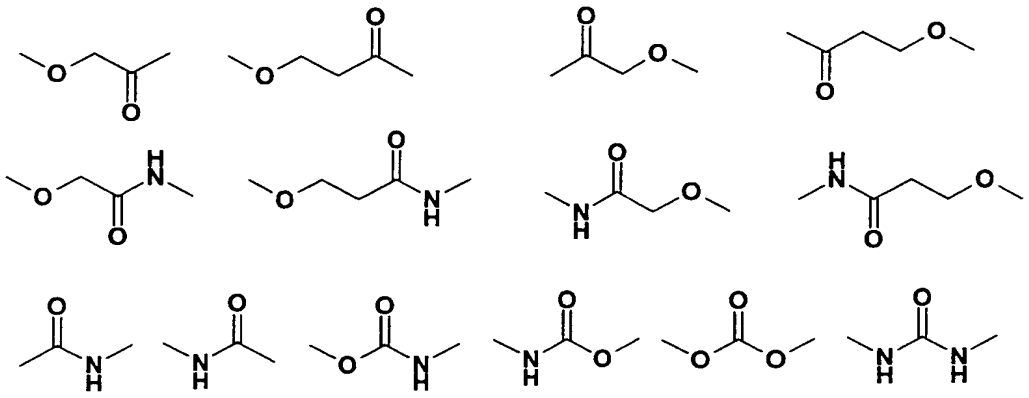
Z1 and Z2 are identical or different and are 1,4-phenylene, 1,3-phenylene, 1,4-naphthylene, 2,6-naphthylene, 1,4-cyclohexylene, 1,3-cyclohexylene, 1,3-cyclopentylene, 1,4-piperazinylene, 4,1-piperidinylene, 1,4-piperidinylene, 2,5-pyrrolidinylene, 4,2-imidazolidinylene, 2,5-furylene, 2,5-pyrrolylene, 4,2-pyridylene, 5,2-pyridylene, 2,5-indolylene, 2,6-indolylene, 3,5-indolylene, 3,6-indolylene, 3,5-indazolylene, 3,6-indazolylene, 2,6-quinolinylene, 2,5-benzofuranylene or 4,2-thiazolylene,

where each arylene, heteroarylene, cycloalkylene, heterocycloalkylene, heteroaryl or heterocycloalkyl may additionally for its part be substituted by one, two or three substituents selected from the group consisting of hydroxyl, halogen, nitro, cyano, amino, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, carboxyl or aminocarbonyl,

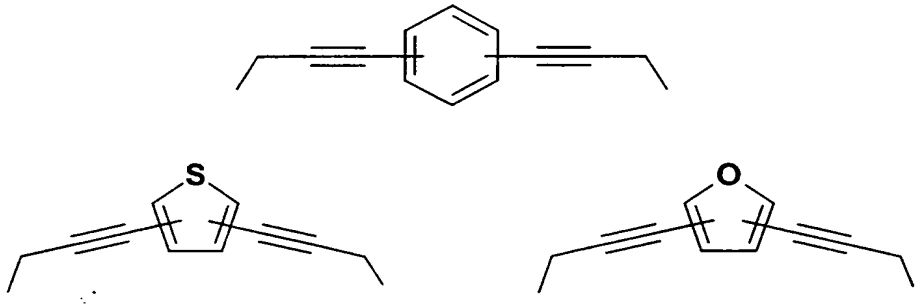
and where on the direct route between the terminal nitrogen atoms 20 to 33 bonds have to be present, the salts of these compounds, and also the N-oxides of the nitrogen-containing heteroaryls, heterocycloalkyls, heteroarylenes and heterocycloalkylenes, and their salts, where all those compounds are

excluded in which one or more of the variables B7, B8, B9, B10, B11 or B12 may assume the meaning of a bond, resulting in the direct linkage of two heteroatoms or carbonyl groups.

Compounds of the formula I of the embodiment a which are to be emphasized are those in which -B1-A1-B3-A3-B5-A5- and -B2-A2-B4-A4-B6-A6- are identical or different and are selected from the groups below



M is a central building block selected from the groups below



K1 is -B7-$(C(O))_m$-B9-Y1 or -B7-$(C(O))_m$-B9-Z1-B11-X1,

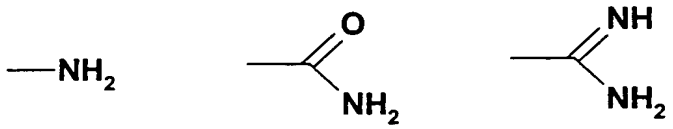
K2 is -B8-$(C(O))_p$-B10-Y2 or -B8-$(C(O))_p$-B10-Z2-B12-X2,

B7, B8, B9, B10, B11 and B12 are identical or different and are a bond or 1-2C-alkylene,

m is 0,

p is 0,

X1 and X2 are identical or different and are selected from the groups below



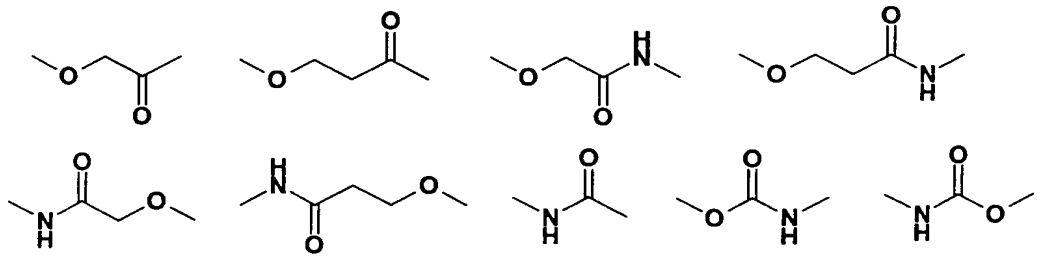
Y1 and Y2 imidazol-1-yl,

Z1 and Z2 are identical or different and are 5,2-pyridinylene, 6-methyl-5,2-pyridinylene, 4,1-piperidinylene, 3,6-indazolylene, 3,6-indolylene, 1,3-phenylene, 1,4-phenylene, 1,3-cyclohexylene or 1,4-cyclohexylene,

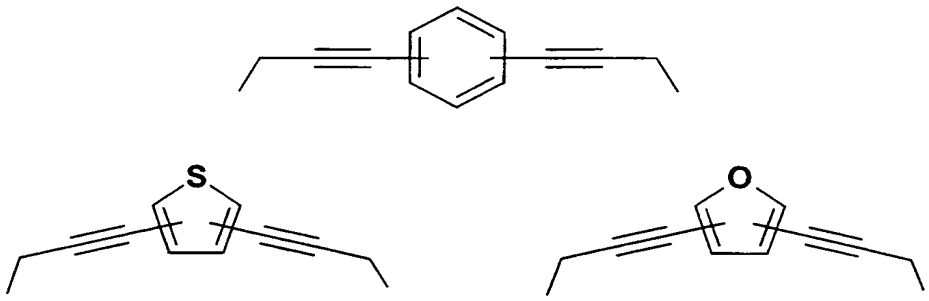
and where on the direct route between the terminal nitrogen atoms 20 to 33 bonds have to be present, the salts of these compounds, and also the N-oxides of the nitrogen-containing heteroaryls, heteroarylenes and heterocycloalkylenes, and their salts.

Compounds of the formula I of the embodiment a which are to be particularly emphasized are those in which

-B1-A1-B3-A3-B5-A5- and -B2-A2-B4-A4-B6-A6- are identical or different and are selected from the groups below



M is a central building block selected from the groups below



K1 is -B7-$(C(O))_m$-B9-Z1-B11-X1,

K2 is -B8-$(C(O))_p$-B10-Z2-B12-X2,

B7 and B8 are identical or different and are 1-2C-alkylene,

B9 and B10 are identical or different and are a bond or 1-2C-alkylene,

B11 and B12 are identical or different and are 1-2C-alkylene,

m is 0,

p is 0,

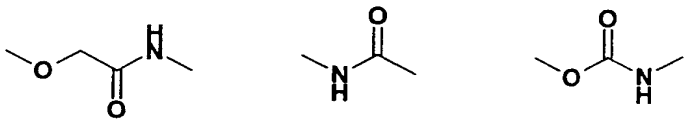
X1 and X2 are amino,

Z1 and Z2 are identical or different and are 1,3-phenylene, 1,4-phenylene, 1,3-cyclohexylene or 1,4-cyclohexylene,

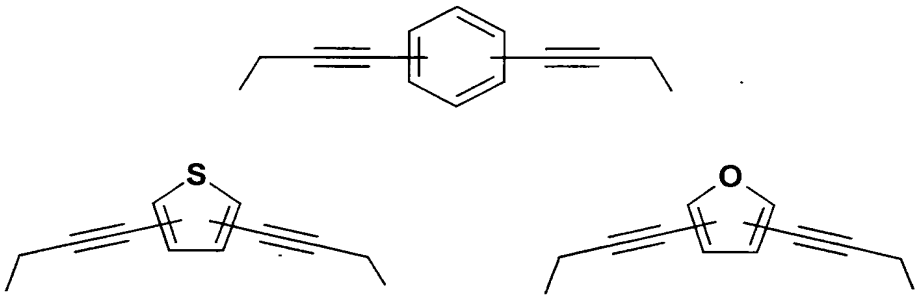
and where on the direct route between the terminal nitrogen atoms 20 to 33 bonds have to be present,

and the salts of these compounds.

Preferred compounds of the formula I of the embodiment a are those in which
-B1-A1-B3-A3-B5-A5- and -B2-A2-B4-A4-B6-A6- are identical or different and are selected from



M is a central building block selected from the group below



K1 is -B7-$(C(O))_m$-B9-Z1-B11-X1,
K2 is -B8-$(C(O))_p$-B10-Z2-B12-X2,
B7 and B8 are methylene,
B9 and B10 are identical or different and are a bond or methylene,
B11 and B12 are methylene,
m is 0,
p is 0,
X1 and X2 are amino,
Z1 and Z2 are identical or different and are 1,4-phenylene or 1,3-phenylene,
and the salts of these compounds.

Particularly preferred compounds of the formula I of the embodiment a are
1,3-Bis-(4-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-benzene;
1,2-Bis-(4-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-benzene;
3,4-Bis-(4-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-thiophene;
2,5-Bis-(4-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-furan;
2,5-Bis-(3-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-furan;
3,4-Bis-(3-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-thiophene;
1,4-Bis-(4-aminomethylbenzylaminocarbonylmethyl-1-oxyprop-2-ynyl)-benzene;
1,3-Bis-(4-aminomethylbenzylaminocarbonylmethyl-1-oxyprop-2-ynyl)-benzene;
1,4-Bis-(4-aminomethylbenzylcarbonyl-1-aminoprop-2-ynyl)-benzene;

1,2-Bis-(4-aminomethylbenzylcarbonyl-1-aminoprop-2-ynyl)-benzene;
1,4-Bis-(4-aminomethylphenylethylcarbonyl-1-aminoprop-2-ynyl)-benzene;
and the salts of these compounds.

The compounds of the formula I are constructed from a large number of building blocks (M, A1, A2, A3, A4, A5, A6, B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, B11, B12, X1, X2, Y1, Y2, Z1 and Z2). In principle, they can be synthesized starting with any of these building blocks. If the compounds of the formula I are constructed largely symmetrically, it is favorable to start the synthesis with the central building block M, whereas in the case of predominantly asymmetrical compounds of the formula I a synthesis starting with one of the end groups K1 or K2 may be advantageous.

Here, the building blocks are linked using always the same pattern, known per se to the person skilled in the art.

It is known to the person skilled in the art that the compounds of the formula I can either be synthesized building block by building block, or by initially constructing relatively large fragments consisting of several individual building blocks, which can then be joined to give the complete molecule.

Owing to the meanings which the individual building blocks of the compounds of the formula I can assume, amino [-NH-], ether [-O-], thioether [-S-], keto [-C(O)-], sulfonyl [-$S(O)_2$-], ester [-C(O)-O-, -O-C(O)-], amide [-C(O)-NH-, -NH-C(O)-], sulfonamide [-SO_2-NH-, -NH-SO_2-], carbamate [-NH-C(O)-O-, -O-C(O)-NH-], carbamide [-NH-C(O)-NH-] or carbonate bridges [-O-C(O)-O-] are present in the compounds of the formula I.

How to prepare such bridges is known per se to the person skilled in the art; suitable methods and starting materials for their preparation are described, for example, in March, Advanced Organic Chemistry, Reactions, Mechanisms and Structure, Third Edition, 1985, John Wiley & Sons.

Ether and thioether bridges can be prepared, for example, by the method of Williamson.

Keto bridges can be introduced, for example, as a component of relatively large building blocks, such as, for example, 1,3-dichloroacetone.

Sulfonyl bridges can be obtained, for example, by oxidation of thioether bridges.

A large number of methods are known for synthesizing ester bridges. Mention may be made here, by way of example, of the reaction of acids with alcohols, preferably using H_2SO_4 or p-toluenesulfonic acid as catalyst; or with the addition of a water-extracting agent, such as a molecular sieve or a carbodiimide. The reaction of acid chlorides with alcohols may also be mentioned at this point.

There is also a large number of known methods for preparing amide bridges. An example which may be mentioned here is the reaction of acyl chlorides with primary or secondary amines. Furthermore, reference is also made to all the methods which have been developed for peptide chemistry. Accordingly, it is possible to construct sulfonamide bridges from sulfonyl chlorides and primary or secondary amines.

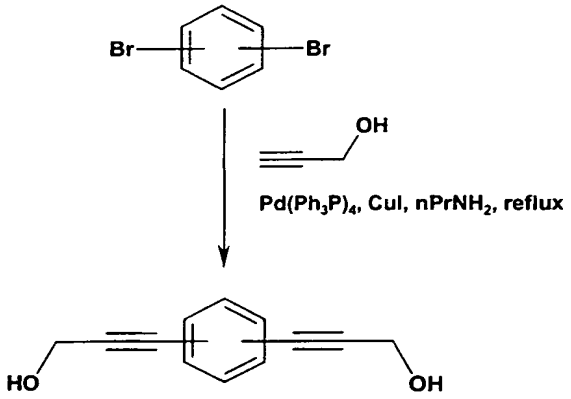
Carbamate bridges can be prepared, for example, by reacting chloroformates with amines. The chloroformates for their part can be synthesized from alcohols and phosgene. A further variant for constructing carbamate bridges is the addition of alcohols to isocyanates.

Similarly to the carbamate bridges, it is possible to prepare carbonate bridges starting from chloroformates, by reaction with alcohols (instead of amines).

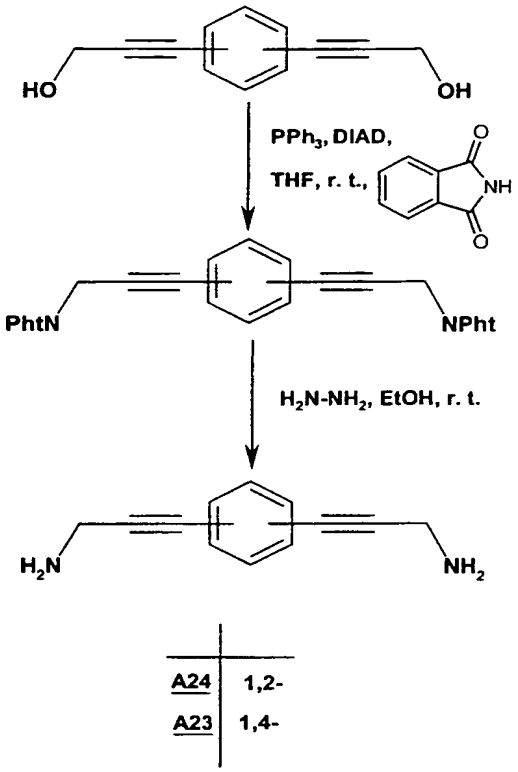
Carbamide bridges can be prepared, for example, by reacting isocyanates with amines.

The preparation of compounds of the formula I is shown in an exemplary manner using the reaction schemes below. Reaction scheme 1 shows the preparation of some exemplary central building blocks. Reaction schemes 2 to 8 show the preparation of exemplary end products. Other compounds of the formula I can be prepared analogously, or by using the abovementioned methods known per se to the person skilled in the art.

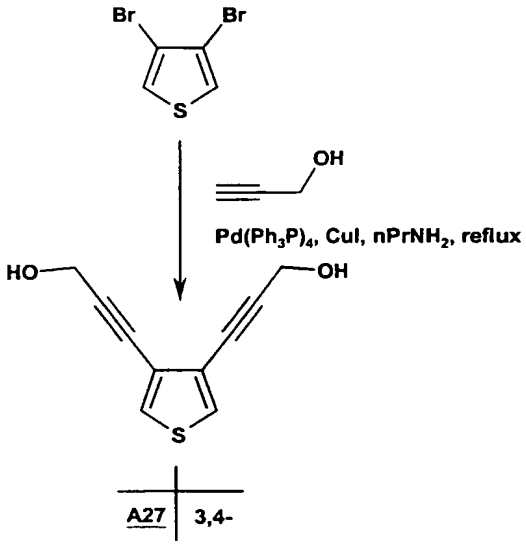
Reaction scheme 1:



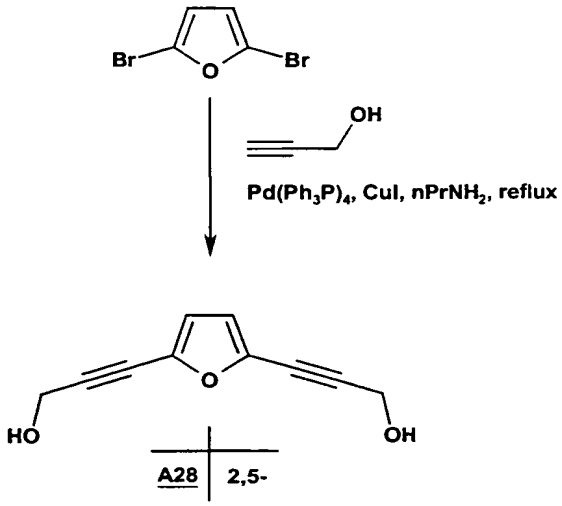
A7	1,2-	(Tetrahedron Lett. 1987, 28 (48), 5981-5984)
A5	1,3-	
A6	1,4-	



A24	1,2-
A23	1,4-

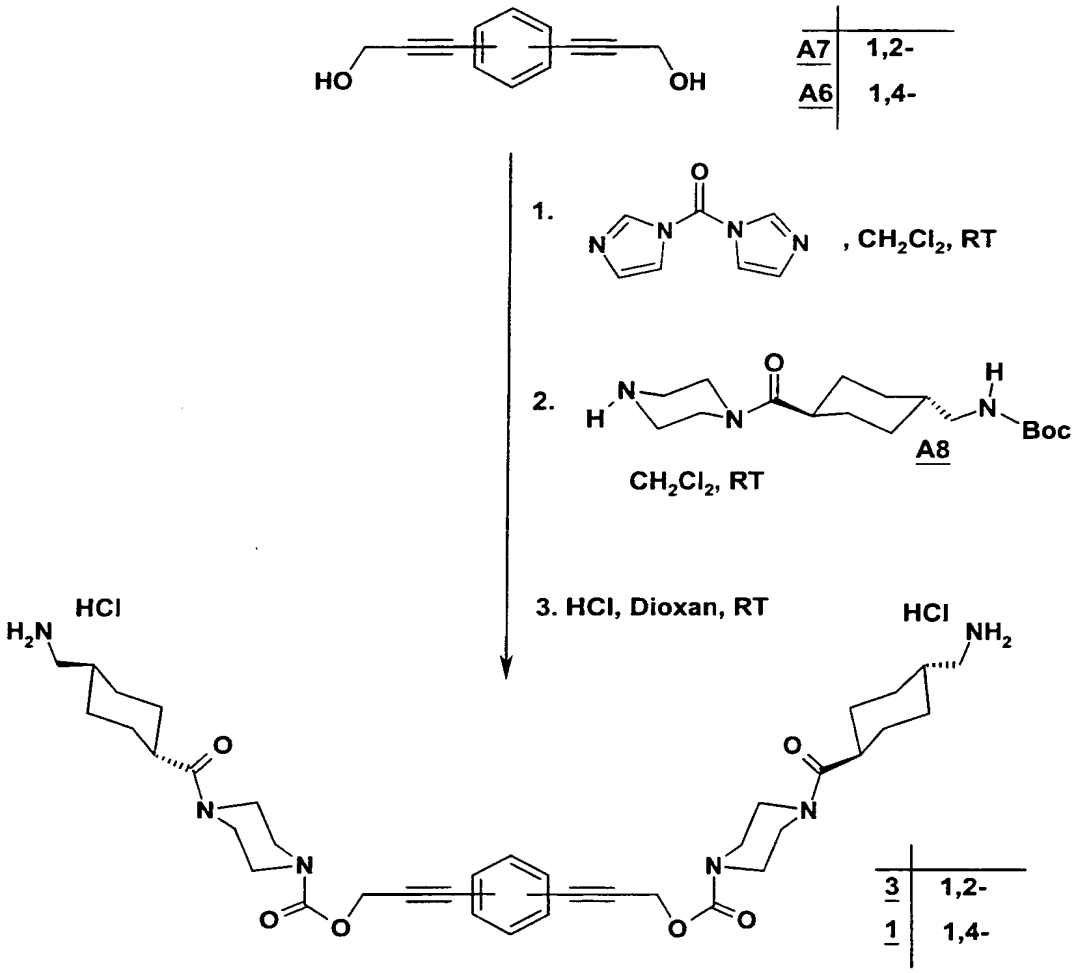


A27	3,4-

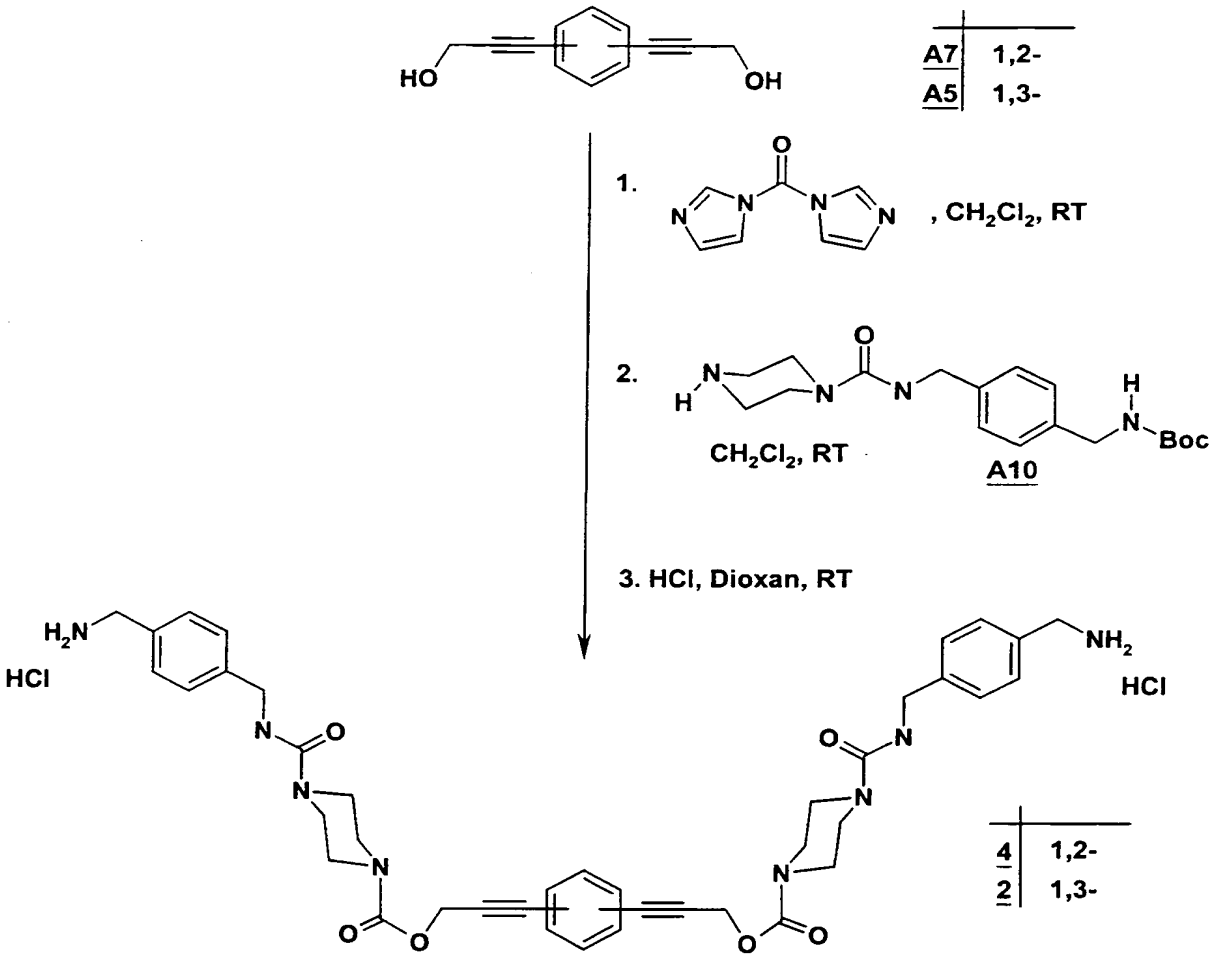


A28	2,5-

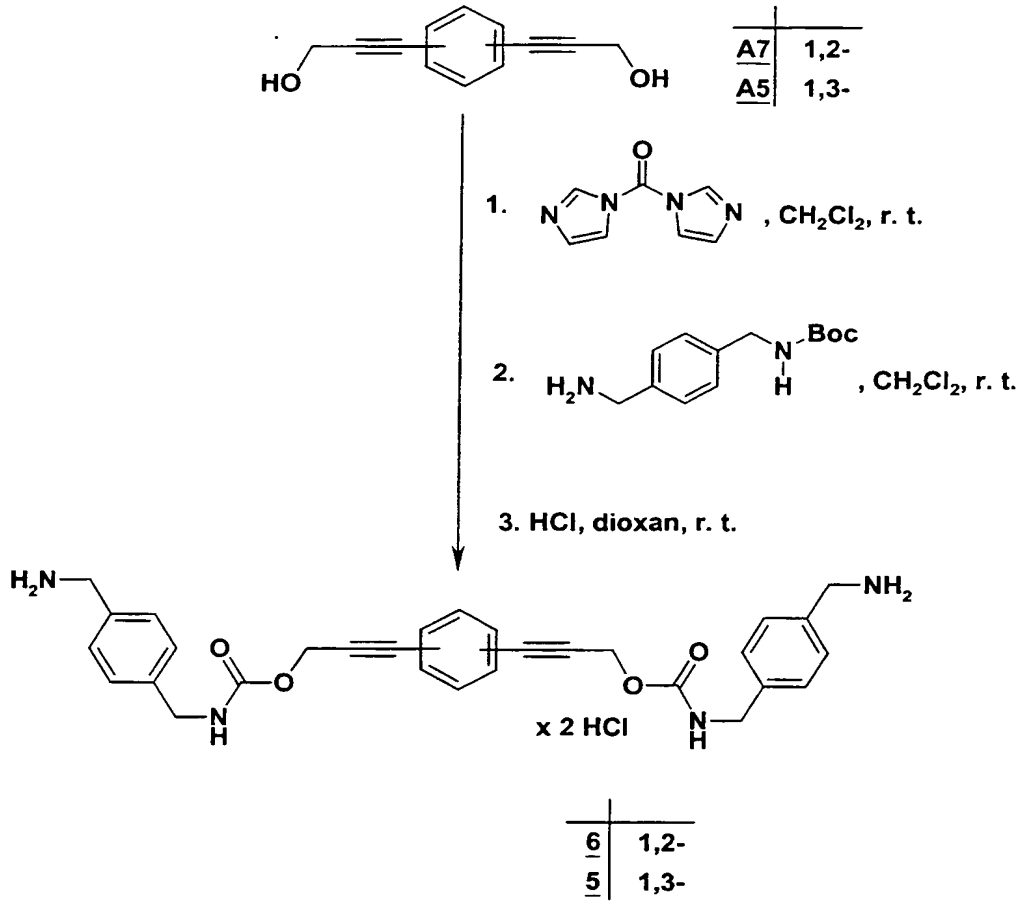
Reaction scheme 2:



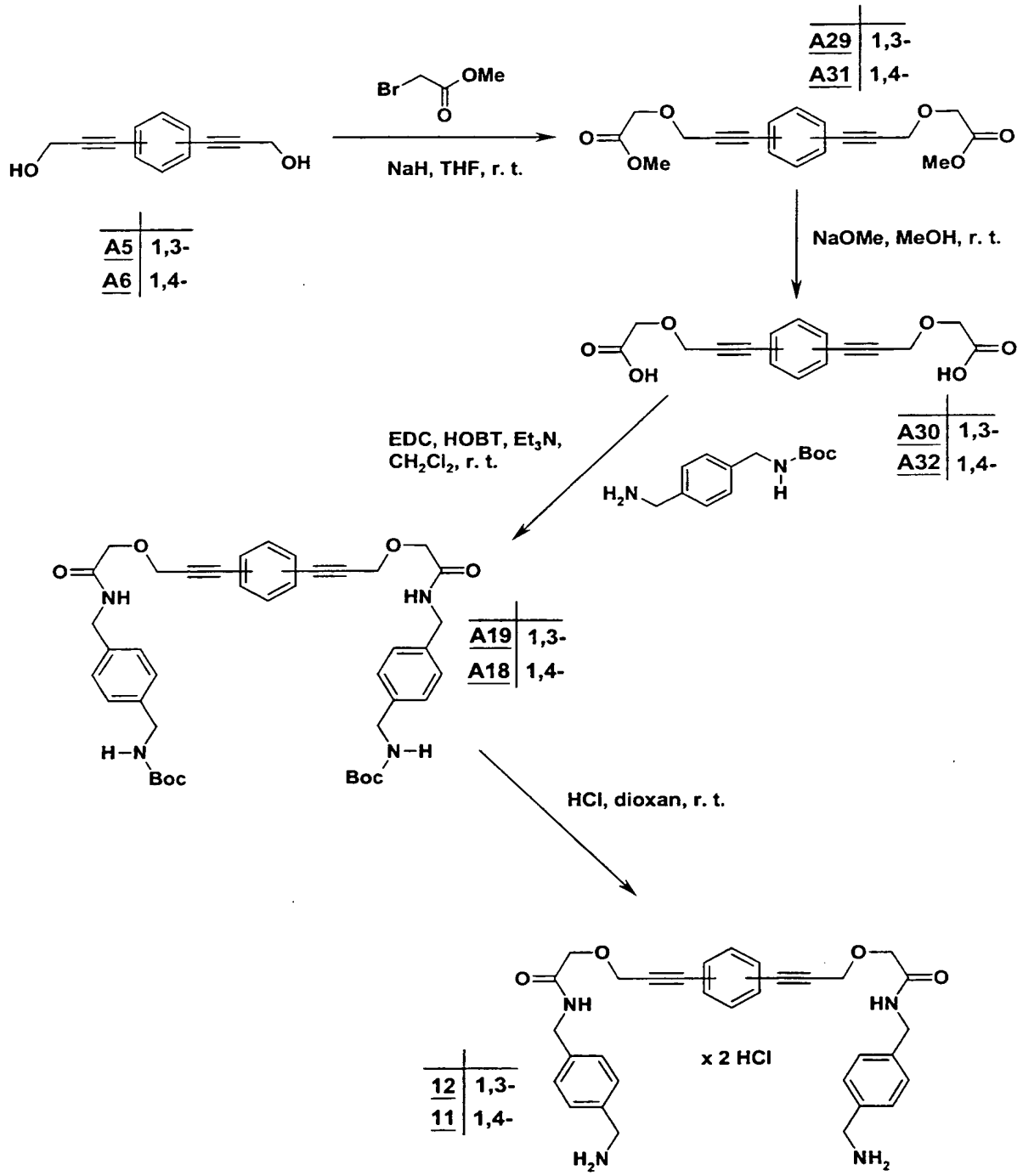
Reaction scheme 3:



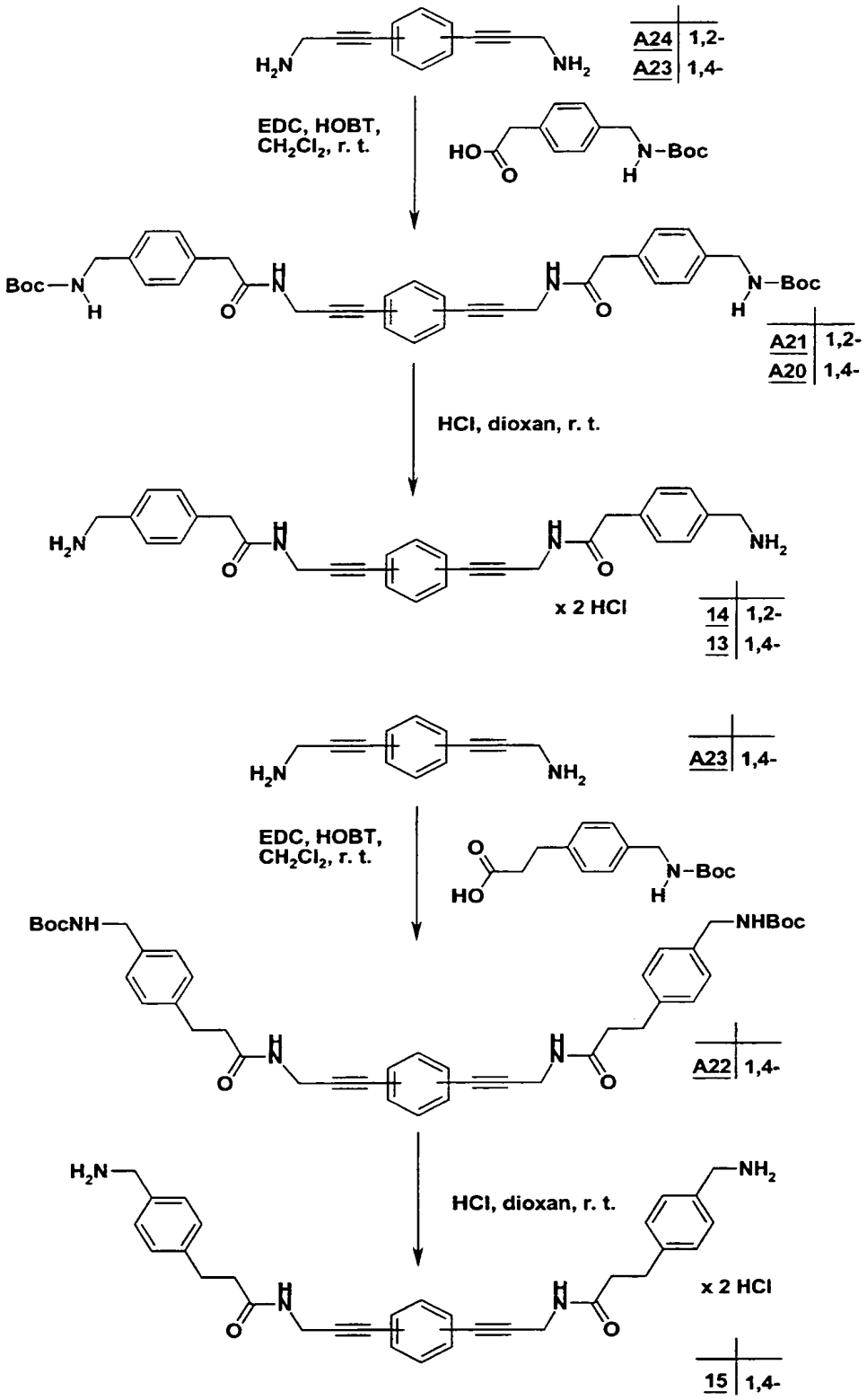
Reaction scheme 4:



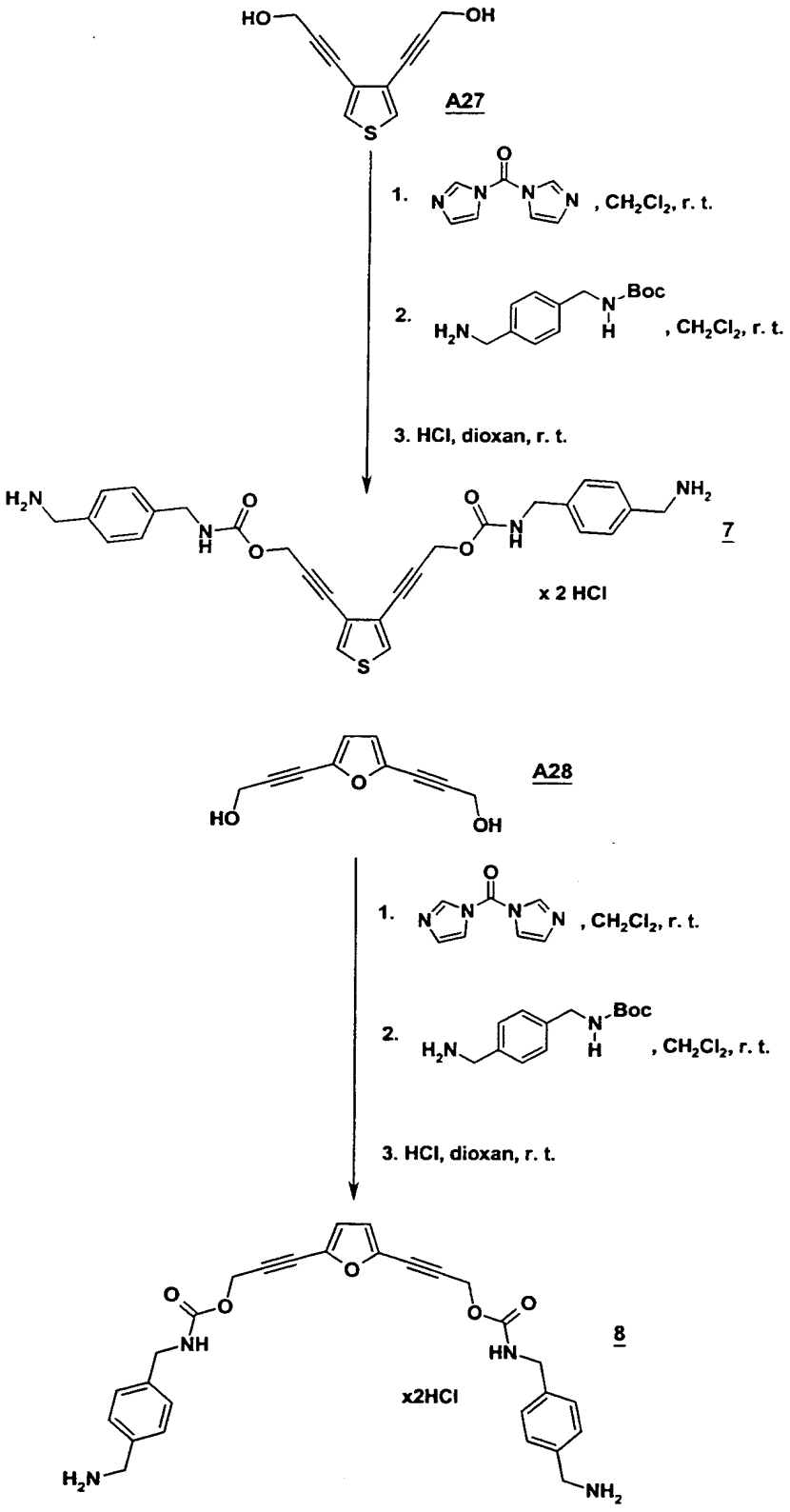
Reaction scheme 5:



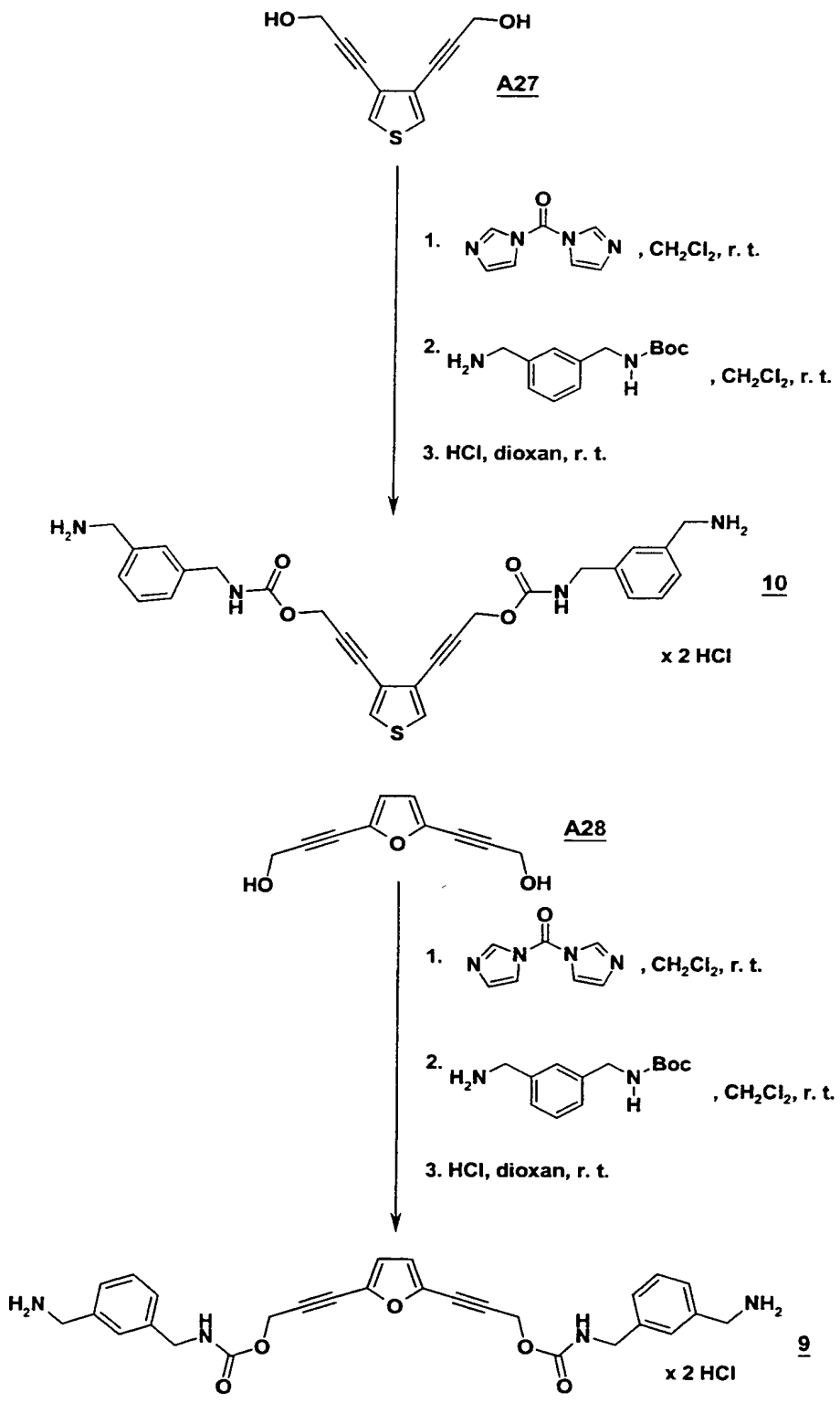
Reaction scheme 6:



Reaction scheme 7:



Reaction scheme 8:



It is also possible to convert compounds of the formula I by derivatization into other compounds of the formula I. Thus, for example, compounds of the formula I having a nitrogen-containing heteroaryl, heteroarylene, heterocycloalkyl or heterocycloalkylene building block can be converted by oxidation into the corresponding N-oxides.

The N-oxidation is carried out in a manner which is likewise known to the person skilled in the art, for example using hydrogen peroxide in methanol or m-chloroperoxybenzoic acid in dichloromethane at room temperature. Which reaction conditions are required in the particular case for carrying out the process is known to the person skilled in the art owing to his expert knowledge.

It is furthermore known to the person skilled in the art that if there are a number of reactive centers on a starting material or intermediate, it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description of the use of a large number of proven protective groups is found, for example, in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

The isolation and purification of the substances according to the invention is carried out in a manner known per se, for example by distilling off the solvent under reduced pressure and recrystallizing the resulting residue from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (for example a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low-molecular-weight aliphatic alcohol, such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this way, pharmacologically unacceptable salts can be converted into pharmacologically acceptable salts.

The examples below serve to illustrate the invention in more detail without restricting it. Likewise, further compounds of the formula I, whose preparation is not explicitly described, can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

In the examples below, the abbreviation RT stands for room temperature, h for hours, min. for minutes, Tol for toluene, Ac for acetone, calc. for calculated, EDC for N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide), DEAD for diethyl azodicarboxylate, HOBT for 1-hydroxy-1H-benzotriazole, TLC for

thin-layer chromatography and MS for mass spectrometry. The compounds mentioned in the examples and their salts are the preferred subject of the invention.

Examples

End products:

General procedure

A solution of the particular Boc-protected bivalent compound (A1-A4, A12-A22; 1.0 mmol) in dioxane (9 ml) is admixed with a saturated solution of HCl in dioxane (5 ml, 22.5 mmol) and stirred at RT for 2-6 h. The resulting precipitate is filtered off under an N_2 atmosphere and washed first with dioxane (2 x 5 ml) and then with diethyl ether (3 x 5 ml). Drying under reduced pressure gives the title compounds (end products 1-15) as colorless solids.

1. **1,4-Bis[4-(trans-4-aminomethylcyclohexylcarbonyl)-1-piperazinylcarbonyl-1-oxyprop-2-ynyl]benzene dihydrochloride**

MS: calc.: $C_{38}H_{52}N_6O_6$ (688.86), found.: [MH^+] 689.3

2. **1,3-Bis[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyprop-2-ynyl]-benzene dihydrochloride**

MS: calc.: $C_{40}H_{46}N_8O_6$ (734.86), found: [MH^+] 735.2

3. **1,2-Bis[4-(trans-4-aminomethylcyclohexylcarbonyl)-1-piperazinylcarbonyl-1-oxyprop-2-ynyl]benzene dihydrochloride**

MS: calc.: $C_{38}H_{52}N_6O_6$ (688.86), found: [MH^+] 689.2

4. **1,2-Bis[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyprop-2-ynyl]-benzene dihydrochloride**

MS: calc.: $C_{40}H_{46}N_8O_6$ (734.86), found: [MH^+] 735.2

5. **1,3-Bis-(4-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-benzene dihydrochloride**

MS: calc.: $C_{30}H_{30}N_4O_4$ (510,60), found: [MH^+] 511,0

6. **1,2-Bis-(4-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-benzene dihydrochloride**

MS: calc.: $C_{30}H_{30}N_4O_4$ (510,60), found: [MH^+] 511,0

7. **3,4-Bis-(4-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-thioph ne dihydrochlori-d**

MS: calc.: $C_{28}H_{28}N_4O_4S$ (516,60), found: $[MH^+]$ 517,0

8. **2,5-Bis-(4-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-furan dihydrochloride**

MS: calc.: $C_{28}H_{28}N_4O_5$ (500,60), found: $[MH^+]$ 501,0

9. **2,5-Bis-(3-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-furan dihydrochloride**

MS: calc.: $C_{28}H_{28}N_4O_5$ (500,60), found: $[MH^+]$ 501,0

10. **3,4-Bis-(3-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-thiophene dihydrochlori-de**

MS: calc.: $C_{28}H_{28}N_4O_4S$ (516,60), found: $[MH^+]$ 517,0

11. **1,4-Bis-(4-aminomethylbenzylaminocarbonylmethyl-1-oxyprop-2-ynyl)-benzene dihydro-chloride**

MS: calc.: $C_{32}H_{34}N_4O_4$ (538,38), found: $[MH^+]$ 539,1

12. **1,3-Bis-(4-aminomethylbenzylaminocarbonylmethyl-1-oxyprop-2-ynyl)-benzene dihydro-chloride**

MS: calc.: $C_{32}H_{34}N_4O_4$ (538,38), found: $[MH^+]$ 539,1

13. **1,4-Bis-(4-aminomethylbenzylcarbonyl-1-aminoprop-2-ynyl)-benzene dihydrochloride**

MS: calc.: $C_{30}H_{30}N_4O_2$ (478,84), found: $[MH^+]$ 479,1

14. **1,2-Bis-(4-aminomethylbenzylcarbonyl-1-aminoprop-2-ynyl)-benzene dihydrochloride**

MS: calc.: $C_{30}H_{30}N_4O_2$ (478,84), found: $[MH^+]$ 479,1

15. **1,4-Bis-(4-aminomethylphenylethylcarbonyl-1-aminoprop-2-ynyl)-benzene dihydrochlori-de**

MS: calc.: $C_{32}H_{34}N_4O_2$ (506,65), found: $[MH^+]$ 507,1

Starting materials:

A1. 1,4-Bis[4-(trans-4-N-tert-butoxycarbonylaminomethylcyclohexylcarbonyl)-1-piperazinyl-carbonyl-1-oxyprop-2-ynyl]benzene

A solution of 3-[4-(3-hydroxyprop-1-ynyl)phenyl]prop-2-yn-1-ol (A6, 0.4 g, 2.14 mmol) in absolute CH_2Cl_2 (10 ml) is admixed with N,N-carbonyldiimidazole (1.04 g, 6.42 mmol) and stirred at RT for 0.5 h. The reaction solution is diluted with CH_2Cl_2 (10 ml) and extracted with a semisaturated aqueous NaCl solution (20 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (10 ml), trans-4-N-tert-butoxycarbonylaminomethylcyclohexylcarbonyl-1-piperazine (A8, 1.53 g, 4.7 mmol) is added and the mixture is stirred at RT overnight. The reaction solution is diluted with CH_2Cl_2 (10 ml) and extracted with a semisaturated aqueous NaCl solution (20 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification is carried out by chromatography [Tol/Ac (7:3)] over a silica gel column. This gives the title compound (1.67 g) as a colorless solid. TLC, silica gel (glass plates), [toluene/acetone (7:3)], R_f = 0.33.

MS: calc.: $C_{48}H_{68}N_6O_{10}$ (889.1), found: $[MH^+]$ 889.0; $[MNa^+]$ 911.2

A2. 1,3-Bis[4-(4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl)-1-piperazinyl-carbonyl-1-oxyprop-2-ynyl]benzene

A solution of 3-[3-(3-hydroxyprop-1-ynyl)phenyl]prop-2-yn-1-ol (A5, 0.4 g, 2.14 mmol) in absolute CH_2Cl_2 (10 ml) is admixed with N,N-carbonyldiimidazole (1.04 g, 6.42 mmol) and stirred at RT for 0.5 h. The reaction solution is diluted with CH_2Cl_2 (10 ml) and extracted with a semisaturated aqueous NaCl solution (20 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (10 ml), 4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl-1-piperazine (A10, 1.64 g, 4.7 mmol) is added and the mixture is stirred at RT overnight. The reaction solution is diluted with CH_2Cl_2 (10 ml) and extracted with a semisaturated aqueous NaCl solution (20 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification is carried out by chromatography [Tol/Ac (8:2)] over a silica gel column. This gives the title compound (1.8 g) as a colorless solid. TLC, silica gel (glass plates), [toluene/acetone (7:3)], R_f = 0.40.

MS: calc.: $C_{50}H_{62}N_8O_{10}$ (934.2), found: $[MH^+]$ 935.0; $[MNa^+]$ 957.3

A3. 1,2-Bis[4-(trans-4-N-tert-butoxycarbonylaminomethylcyclohexylcarbonyl)-1-piperazinyl-carbonyl-1-oxyprop-2-ynyl]benzen

A solution of 3-[2-(3-hydroxyprop-1-ynyl)phenyl]prop-2-yn-1-ol (A7, 0.4 g, 2.14 mmol) in absolute CH_2Cl_2 (10 ml) is admixed with N,N-carbonyldiimidazole (1.04 g, 6.42 mmol) and stirred at RT for 0.5 h. The reaction solution is diluted with CH_2Cl_2 (10 ml) and extracted with a semisaturated aqueous NaCl solution (20 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (10 ml), trans-4-N-tert-butoxy-carbonylaminomethylcyclohexylcarbonyl-1-piperazine (A8, 1.53 g, 4.7 mmol) is added and the mixture is stirred at RT overnight. The reaction solution is diluted with CH_2Cl_2 (10 ml) and extracted with a semisaturated aqueous NaCl solution (20 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification is carried out by chromatography [Tol/Ac (8:2)] over a silica gel column. This gives the title compound (1.4 g) as an amorphous solid. TLC, silica gel (glass plates), [toluene/acetone (7:3)], R_f = 0.40.

MS: calc.: $C_{48}H_{68}N_6O_{10}$ (889.1), found: $[MH^+]$ 889.0; $[MNa^+]$ 911.3

A4. 1,2-Bis[4-(4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl)-1-piperazinyl-carbonyl-1-oxyprop-2-ynyl]benzene

A solution of 3-[2-(3-hydroxyprop-1-ynyl)phenyl]prop-2-yn-1-ol (A7, 0.4 g, 2.14 mmol) in absolute CH_2Cl_2 (10 ml) is admixed with N,N-carbonyldiimidazole (1.04 g, 6.42 mmol) and stirred at RT for 0.5 h. The reaction solution is diluted with CH_2Cl_2 (10 ml) and extracted with a semisaturated aqueous NaCl solution (20 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (10 ml), 4-N-tert-butoxycarbon-ylaminomethylbenzylaminocarbonyl-1-piperazine (A10, 1.63 g, 4.7 mmol) is added and the mixture is stirred at room temperature overnight. The reaction solution is diluted with CH_2Cl_2 (10 ml) and extracted with a semisaturated aqueous NaCl solution (20 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification is carried out by chromatography [Tol/Ac (6:4)] over a silica gel column. This gives the title compound (1.1 g) as a colorless resin. TLC, silica gel (glass plates), [toluene/acetone (7:3)], R_f = 0.16.

MS: calc.: $C_{50}H_{62}N_8O_{10}$ (934.2), found: $[MH^+]$ 935.0; $[MNa^+]$ 957.3

A5. 3-[3-(3-Hydroxyprop-1-ynyl)phenyl]prop-2-yn-1-ol

A solution of 1,3-dibromobenzene (0.6 ml, 5.0 mmol) in n-propylamine (15 ml) is admixed successively with $Pd(Ph_3P)_4$ (116 mg, 2 %), CuI (28 mg, 3 %) and propargyl alcohol (0.9 ml, 15 mmol) and stirred at RT for 20 h. More $Pd(Ph_3P)_4$ (58 mg, 1 %), CuI (14 mg, 1.5%) and propargyl alcohol (0.45 ml, 7.5 mmol) are then added, and the mixture is stirred at reflux for a further 6.5 h. After cooling, the

reaction mixture is filtered off with suction over kieselguhr, and the filter cake is washed with ethyl acetate (20 ml). The organic phase is concentrated under reduced pressure. Further purification is carried out by chromatography [Tol/Ac (8:2)] over a silica gel column. This gives the title compound (0.6 g) as a colorless oil. TLC, silica gel (glass plates), [toluene/acetone (8:2)], R_f = 0.22.

MS: calc.: $C_{12}H_{10}O_2$ (186.2), found: [M^+] 186.0

A6. 3-[4-(3-Hydroxyprop-1-ynyl)phenyl]prop-2-yn-1-ol

A solution of 1,4-dibromobenzene (1.18 g, 5.0 mmol) in n-propylamine (15 ml) is admixed successively with $Pd(Ph_3P)_4$ (116 mg, 2 %), CuI (28 mg, 3 %) and propargyl alcohol (0.9 ml, 15 mmol) and stirred at RT for 1 h and then at reflux for 7 h. More $Pd(Ph_3P)_4$ (58 mg, 1 %), CuI (14 mg, 1.5 %) and propargyl alcohol (0.45 ml, 7.5 mmol) are then added, and the mixture is stirred at reflux for a further 8 h. After cooling, the reaction mixture is filtered off with suction over kieselguhr and the filter cake is washed with ethyl acetate (20 ml). The organic phase is concentrated under reduced pressure. Further purification is carried out by chromatography [Tol/Ac (8:2)] over a silica gel column. This gives the title compound (0.84 g) as a colorless solid. TLC, silica gel (glass plates), [toluene/acetone (8:2)], R_f = 0.22.

MS: calc.: $C_{12}H_{10}O_2$ (186.2), found: [M^+-H] 185.0; [M^+] 186.0

A7. 3-[2-(3-Hydroxyprop-1-ynyl)phenyl]prop-2-yn-1-ol

Tetrahedron Letters, 1987, 28 (48), 5981-5984

A8. Trans-4-N-tert-butoxycarbonylaminomethylcyclohexylcarbonyl-1-piperazine

At RT, benzyl 4-{1-[trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexyl]carbonyl}piperazine-1-carboxylate (A9, 0.4 g, 0.87 mmol) is dissolved in MeOH (20 ml) and admixed with palladium-on-carbon (10% Pd, 0.2 g). Under an atmosphere of hydrogen and at RT, the mixture is stirred in a circulation hydrogenation apparatus for 3 h. After uniform conversion (TLC), the catalyst is filtered off and the solution is concentrated under reduced pressure. This gives the title compound (0.28 g) as a colorless solid. Without any further purification, the compound could be used for the next step. TLC, silica gel, glass plates, [CH_2Cl_2/ MeOH (9:1)], R_f = 0.10.

A9. Benzyl 4-{1-[trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexyl]carbonyl}piperazine-1-carboxylate

A solution of trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexanecarboxylic acid (0.40 g, 1.55 mmol) and benzyloxycarbonyl-1-piperazine (0.34 g, 1.55 mmol) in absolute CH_2Cl_2 (9 ml) and Et_3N (0.96 ml) is admixed with HOBT (0.16 g, 1.2 mmol) and stirred at RT for 20 min. EDC (0.23 g, 1.2

mmol) is then added, and the mixture is stirred at RT overnight. The reaction solution is diluted with CH_2Cl_2 (15 ml) and extracted (2 x) with semisaturated aqueous NH_4Cl solution (15 ml), dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification by chromatography [CH_2Cl_2/ MeOH (9:1)] over a silica gel column gives the title compound (0.71 g) as a colorless powder. TLC, silica gel, glass plates [CH_2Cl_2/ MeOH (9:1)], R_f = 0.24.

A10. 1-[4-(tert-Butyloxycarbonylaminomethyl)benzylaminocarbonyl]piperazine

41.7 g (86.4 mmol) of benzyl 4-[4-(tert-butyloxycarbonylaminomethyl)benzylaminocarbonyl]piperazine-1-carboxylate (starting material A11) in 1.0 l of methanol are hydrogenated over palladium/carbon (5%) for 4 h. The catalyst is filtered off and the solvent is removed, giving 30.3 g of the title compound as a colorless oil.

A11. Benzyl-4-[4-(tert-butyloxycarbonylaminomethyl)benzylaminocarbonyl]piperazine-1-carboxylate

At 0°C, 25.0 g (106 mmol) of 4-(tert-butyloxycarbonylaminomethyl)benzylamine in 150 ml of dichloromethane are added dropwise to a solution of 22.4 g (111 mmol) of 4-nitrophenyl chloroformate in 200 ml of dichloromethane, and the mixture is stirred for 10 min. 15.6 ml (111 mmol) of triethylamine are then added dropwise, and the mixture is stirred at RT for 1.5 h. At 0°C, initially 24.5 g (111 mmol) of benzyl piperazine-1-carboxylate in 80 ml of dichloromethane and then 15.6 ml (111 mmol) of triethylamine are added dropwise. The mixture is stirred at RT for 16 h. The solvent is removed from the reaction mixture and the crude product is chromatographed over silica gel (toluene/ethyl acetate = 1:1). Crystallization from diisopropyl ether gives 41.7 g of the title compound as a colorless solid of m.p. 108-112°C.

A12. 3,4-Bis-(4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-thiophene

N,N-Carbonyldiimidazol (1.6 g, 9.88 mmol) is added to a solution of 3-[4-(3-hydroxyprop-1-ynyl)thiophene]prop-2-yn-1-ol (A27, 0.4 g, 2.08 mmol) in absolute CH_2Cl_2 (15 ml), and the mixture is stirred at RT for 1.5 h. The reaction solution is diluted with CH_2Cl_2 (15 ml) and extracted with a semisaturated aqueous NaCl solution (20 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (15 ml), 4-N-tert-butoxycarbonylaminomethylbenzylamine (1.13 g, 4.8 mmol) is added and the mixture is stirred at RT overnight. The resulting precipitate is filtered off with suction, washed with CH_2Cl_2 (10 ml) and dried under reduced pressure. This gives the title compound (0.65 g) as a colorless solid. TLC, silica gel (glass plates), [toluene/acetone (7:3)], R_f = 0.42.

MS: calc.: $C_{38}H_{44}N_4O_8S$ (716.1), found: [MNH_4^+] 733.8; [MNa^+] 739.0

A13. 3,4-Bis-(3-N-tert-butoxycarb nylaminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-thiophene

N,N-Carbonyldiimidazol (1.6 g, 9.88 mmol) is added to a solution of 3-[4-(3-hydroxyprop-1-ynyl)thiophene]prop-2-yn-1-ol (A27, 0.4 g, 2.08 mmol) in absolute CH_2Cl_2 (15 ml), and the mixture is stirred at RT for 1.5 h. The reaction solution is diluted with CH_2Cl_2 (15 ml) and extracted with a semisaturated aqueous NaCl solution (20 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (15 ml), 3-N-tert-butoxycarbonylaminomethylbenzylamine (1.13 g, 4.8 mmol) is added and the mixture is stirred at RT overnight. The resulting precipitate is filtered off with suction, washed with CH_2Cl_2 (10 ml) and dried under reduced pressure. This gives the title compound (0.62 g) as a colorless solid. TLC, silica gel (glass plates), [toluene/acetone (7:3)], R_f = 0.31.

MS: calc.: $C_{38}H_{44}N_4O_8S$ (716.1), found: $[MNH_4^+]$ 733.8

A14. 1,3-Bis-(4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-benzene

N,N-Carbonyldiimidazole (1.33 g, 8.21 mmol) is added to a solution of 3-[3-(3-hydroxyprop-1-ynyl)phenyl]prop-2-yn-1-ol (A5, 0.5 g, 2.7 mmol) in absolute CH_2Cl_2 (10 ml), and the mixture is stirred at RT for 1 h. The reaction solution is diluted with CH_2Cl_2 (15 ml) and extracted with a semisaturated aqueous NaCl solution. The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (10 ml), 4-N-tert-butoxycarbonylaminomethylbenzylamine (1.4 g, 5.9 mmol) is added and the mixture is stirred at RT overnight. The reaction mixture is then admixed with Et_2O (10 ml) and stirred at RT for 0.5 h. The resulting precipitate is filtered off with suction, washed with CH_2Cl_2/Et_2O/MeOH (1:1:0.5; 10 ml) and dried under reduced pressure. This gives the title compound (1.67 g) as a colorless solid. TLC, silica gel (glass plates) [toluene/acetone (7:3)], R_f = 0.25.

MS: calc.: $C_{40}H_{46}N_4O_8$ (710.1), found: $[MNa^+]$ 733.2

A15. 1,2-Bis-(4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-benzene

N,N-Carbonyldiimidazole (1.33 g, 8.21 mmol) is added to a solution of 3-[2-(3-hydroxyprop-1-ynyl)phenyl]prop-2-yn-1-ol (A7, 0.5 g, 2.7 mmol) in absolute CH_2Cl_2 (10 ml), and the mixture is stirred at RT for 1 h. The reaction solution is diluted with CH_2Cl_2 (15 ml) and extracted with a semisaturated aqueous NaCl solution. The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (10 ml), 4-N-tert-butoxycarbonylamino-

methylbenzylamine (1.4 g, 5.9 mmol) is added and the mixture is stirred at RT overnight. The reaction mixture is then admixed with Et_2O (10 ml) and stirred at RT for 0.5 h. The resulting precipitate is filtered off with suction, washed with CH_2Cl_2/Et_2O/MeOH (1:1:0.5; 10 ml) and dried under reduced pressure. This gives the title compound (1.0 g) as a colorless solid. TLC, silica gel (glass plates) [toluene/acetone (7:3)], R_f = 0.20.

MS: calc.: $C_{40}H_{46}N_4O_8$ (710.1), found: [MNa^+] 733.1

A16. 2,5-Bis-(4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-furan

N,N-Carbonyldiimidazole (1.12 g, 6.91 mmol) is added to a solution of 3-[5-(3-hydroxyprop-1-ynyl)furan]prop-2-yn-1-ol (A28, 0.4 g, 2.27 mmol) in absolute CH_2Cl_2 (8 ml), and the mixture is stirred at RT for 1 h. The reaction solution is diluted with CH_2Cl_2 (8 ml) and extracted with a semisaturated aqueous NaCl solution (15 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (8 ml), 4-N-tert-butoxycarbonylaminomethylbenzylamine (1.18 g, 5.0 mmol) is added and the mixture is stirred at RT overnight. The reaction mixture is then admixed with Et_2O (8 ml) and stirred at RT for 0.5 h. The resulting precipitate is filtered off with suction, washed with CH_2Cl_2/Et_2O/MeOH (1:1:0.5; 8 ml) and dried under reduced pressure. This gives the title compound (1.1 g) as a colorless solid. TLC, silica gel (glass plate), [toluene/acetone (7:3)], R_f = 0.23.

MS: calc.: $C_{38}H_{44}N_4O_9$ (700.2), found: [MNH_4^+] 717.8; [MNa^+] 723.1

A17. 2,5-Bis-(3-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-furan

N,N-Carbonyldiimidazole (1.12 g, 6.91 mmol) is added to a solution of 3-[5-(3-hydroxyprop-1-ynyl)furan]prop-2-yn-1-ol (A28, 0.4 g, 2.27 mmol) in absolute CH_2Cl_2 (8 ml), and the mixture is stirred at RT for 1 h. The reaction solution is diluted with CH_2Cl_2 (8 ml) and extracted with a semisaturated aqueous NaCl solution (15 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (8 ml), 3-N-tert-butoxycarbonylaminomethylbenzylamine (1.18 g, 5.0 mmol) is added and the mixture is stirred at RT overnight. The reaction solution is diluted with CH_2Cl_2 (10 ml) and extracted with a semisaturated aqueous NaCl solution (20 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification is carried out by chromatography [Tol/Ac (8:2)] over a silica gel column. This gives the title compound (0.7 g) as a colorless solid. TLC, silica gel (glass plates), [toluene/acetone (8:2)], R_f = 0.40.

MS: calc.: $C_{38}H_{44}N_4O_9$ (700.2), found: [MNH_4^+] 717.9; [MH^+] 700.9

A18. 1,4-Bis-(4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonylmethyl-1-oxyprop-2-ynyl)benzene

HOBT (1.45 g, 10.9 mmol) is added to a solution of {3-[4-(3-carboxymethoxyprop-1-ynyl)phenyl]prop-2-ynyloxy}acetic acid (A32, 0.40 g, 1.3 mmol) and 4-N-tert-butoxycarbonylaminomethylbenzylamine (2.33 g, 9.9 mmol) in absolute CH_2Cl_2 (20 ml) and Et_3N (2.5 ml), and the mixture is stirred at RT for 45 min. EDC (2.1 g, 10.9 mmol) is then added, and the mixture is stirred at RT overnight. The reaction solution is diluted with CH_2Cl_2 (15 ml) and extracted (2 ×) with semisaturated aqueous NH_4Cl solution (25 ml), dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification by chromatography [Tol/Ac (8:2)] over a silica gel column gives the title compound (0.75 g) as a colorless powder. TLC, silica gel, glass plates, [Tol/Ac (7:3)], R_f = 0.5.

MS: calc.: $C_{42}H_{50}N_4O_8$ (738.0), found: [MH^+-Boc] 639.1, MH^+-2Boc] 539.2

A19. 1,3-Bis-(4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonylmethyl-1-oxyprop-2-ynyl)benzene

HOBT (1.45 g, 10.9 mmol) is added to a solution of {3-[3-(3-carboxymethoxyprop-1-ynyl)phenyl]prop-2-ynyloxy}acetic acid (A30, 0.40 g, 1.3 mmol) and 4-N-tert-butoxycarbonylaminomethylbenzylamine (1.2 g, 5.2 mmol) in absolute CH_2Cl_2 (20 ml) and Et_3N (2.5 ml), and the mixture is stirred at RT for 45 min. EDC (2.1 g, 10.9 mmol) is then added, and the mixture is stirred at RT overnight. The reaction solution is diluted with CH_2Cl_2 (15 ml) and extracted (2 ×) with semisaturated aqueous NH_4Cl solution (25 ml), dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification by chromatography [Tol/Ac (8:2)] over a silica gel column gives the title compound (1.1 g) as a colorless powder. TLC, silica gel, glass plates, [Tol/Ac (7:3)], R_f = 0.51.

MS: calc.: $C_{42}H_{50}N_4O_8$ (738.0), found: [MH^+] 738.8, [MNH_4^+] 755.8; [MNa^+] 761.2

A20. 1,4-Bis-(4-N-tert-butoxycarbonylaminomethylbenzylcarbonyl-1-aminoprop-2-ynyl)-benzene

HOBT (2.17 g, 16.3 mmol) is added to a solution of [4-(tert-butoxycarbonylaminomethyl)phenyl]acetic acid (2.6 g, 9.8 mmol) and 3-[4-(3-aminoprop-1-ynyl)phenyl]prop-2-ynylamine (A23, 0.45 g, 2.44 mmol) in absolute CH_2Cl_2 (10 ml) and Et_3N (3.8 ml), and the mixture is stirred at RT for 45 min. EDC (3.1 g, 16.1 mmol) is then added, and the mixture is stirred at RT overnight. The reaction solution is diluted with CH_2Cl_2 (15 ml) and extracted (2 ×) with semisaturated aqueous NH_4Cl solution (25 ml), dried over $MgS0_4$, filtered off and concentrated under reduced pressure. Further purification by chromatography [Tol/Ac (7:3)] over a silica gel column gives the title compound (0.25 g) as a colorless powder. TLC, silica gel, glass plates [Tol/Ac (7:3)], R_f = 0.49.

MS: calc.: $C_{40}H_{46}N_4O_6$ (678.6), found: [MNa^+] 701.1

A21. 1,2-Bis-(4-N-tert-butoxycarbonylaminomethylbenzylcarbonyl-1-aminoprop-2-ynyl)-benzene

HOBT (1.45 g, 7.7 mmol) is added to a solution of [4-(tert-butoxycarbonylaminomethyl)phenyl]acetic acid (1.73 g, 6.52 mmol) and 3-[2-(3-aminoprop-1-ynyl)phenyl]prop-2-ynylamine (A24, 0.3 g, 1.63 mmol) in absolute CH_2Cl_2 (7 ml) and Et_3N (2.5 ml), and the mixture is stirred at RT for 45 min. EDC (2.06 g, 7.7 mmol) is then added and the mixture is stirred at RT overnight. The reaction solution is diluted with CH_2Cl_2 (7 ml) and extracted (2 ×) with semisaturated aqueous NH_4Cl solution (25 ml), dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification by chromatography [Tol/Ac (8:2)] over a silica gel column gives the title compound (0.23 g) as a colorless powder. TLC, silica gel, glass plates [Tol/Ac (6:4)], R_f = 0.36.

MS: calc.: $C_{40}H_{46}N_4O_6$ (678.6), found: [MH^+] 678.7, [MNa^+] 701.1

A22. 1,4-Bis-(4-N-tert-butoxycarbonylaminomethylphenylethylcarbonyl-1-aminoprop-2-ynyl)-benzene

HOBT (1.27 g, 6.7 mmol) is added to a solution of 3-[4-(tert-butoxycarbonylaminomethyl)phenyl] propionic acid (A33, 1.0 g, 3.58 mmol) and 3-[4-(3-aminoprop-1-ynyl)phenyl]prop-2-ynylamine (A23, 0.26 g, 1.41 mmol) in absolute CH_2Cl_2 (10 ml) and Et_3N (2.5 ml), and the mixture is stirred at RT for 45 min. EDC (1.82 g, 6.8 mmol) is then added, and the mixture is stirred at RT overnight. The reaction solution is diluted with CH_2Cl_2 (7 ml) and extracted (2 ×) with semisaturated aqueous NH_4Cl solution (25 ml), dried over $MgS0_4$, filtered off and concentrated under reduced pressure. Further purification by chromatography [Tol/Ac (8:2)] over a silica gel column gives the title compound (0.42 g) as a colorless powder. TLC, silica gel, glass plates [Tol/Ac (8:2)], R_f = 0.48.

MS: calc.: $C_{42}H_{50}N_4O_6$ (706.9), found: [MNa^+] 729.0

A23. 3-[4-(3-Aminoprop-1-ynyl)phenyl]prop-2-ynylamine

At RT, hydrazine hydrate (5.1 ml) is added dropwise to a suspension of 1,4-bis-(1-phthalimidoprop-2-ynyl)benzene (A25, 7.8 g, 17.5 mmol) in ethanol (200 ml), and the solution is heated at the boil for 2.5 h. The reaction solution is stirred at RT overnight and then concentrated under reduced pressure. The residue is taken up in CH_2Cl_2 (150 ml) and extracted (3 ×) with aqueous 1 N NaOH solution (150 ml). The combined organic phases are dried over $MgSO_4$, filtered off and concentrated under reduced pressure. This gives the title compound (3 g) as a yellow oil. The compound is used without further purification for the next step.

A24. 3-[2-(3-Aminoprop-1-ynyl)phenyl]prop-2-ynylamine

At RT, hydrazine hydrate (1.1 ml) is added dropwise to a suspension of 1,2-bis-(1-phthalimidoprop-2-ynyl)benzene (A26, 1.5 g, 3.37 mmol) in ethanol (25 ml), and the solution is heated at the boil for 2.5 h. The reaction solution is stirred at RT overnight and then concentrated under reduced pressure. The residue is taken up in CH_2Cl_2 (20 ml) and extracted (3 ×) with aqueous 1 N NaOH solution (20 ml). The combined organic phases are dried over $MgSO_4$, filtered off and concentrated under reduced pressure. This gives the title compound (0.6 g) as a yellow oil. The compound is used without further purification for the next step.

A25. 1,4-Bis-(1-phthalimidoprop-2-ynyl)benzene

Triphenylphosphine (3.3 g, 12.7 mmol) and phthalimide (1.9 g, 13.5 mmol) are added successively to a solution of 3-[4-(3-hydroxyprop-1-ynyl)phenyl]prop-2-yn-1-ol (A6, 1.2 g, 6.4 mmol) in absolute THF (30 ml). DEAD (2.7 ml, 12.7 mmol) is then added dropwise to the reaction mixture. The mixture is stirred at RT for 2 d and the resulting precipitate is then filtered off and washed with THF (15 ml) and Et_2O (15 ml). The title compound (1.5 g) is obtained as a colorless powder. TLC, silica gel, glass plates, [Tol/Ac (8:2)], R_f = 0.51.

A26. 1,2-Bis-(1-phthalimidoprop-2-ynyl)benzene

Triphenylphosphine (1.6 g, 6.3 mmol) and phthalimide (1.0 g, 6.7 mmol) are added successively to a solution of 3-[2-(3-hydroxyprop-1-ynyl)phenyl]prop-2-yn-1-ol (A7, 0.6 g, 3.2 mmol) in absolute THF (20 ml). DEAD (1.35 ml, 6.3 mmol) is then added dropwise to the reaction mixture. The mixture is stirred at RT for 2 d and the resulting precipitate is then filtered off and washed with THF (8 ml) and Et_2O (8 ml). The title compound (0.97 g) is obtained as a colorless powder. TLC, silica gel, glass plates, [Tol/Ac (8:2)], R_f = 0.60.

A27. 3-[4-(3-Hydroxyprop-1-ynyl)thiophen-3-yl]prop-2-yn-1-ol

$Pd(Ph_3P)_4$ (116 mg, 2%), CuI (28 mg, 3%) and propargyl alcohol (0.9 ml, 15 mmol) are added successively to a solution of 3,4-dibromothiophene (1.18 g, 5.0 mmol) in n-propylamine (15 ml), and the reaction mixture is stirred at RT for 1 h and then under reflux for 7 h. More $Pd(Ph_3P)_4$ (58 mg, 1%), CuI (14 mg, 1.5%) and propargyl alcohol (0.45 ml, 7.5 mmol) are then added and the mixture is stirred under reflux for another 8 h. After cooling, the reaction mixture is filtered off through kieselguhr and washed with ethyl acetate (20 ml). The organic phase is concentrated under reduced pressure. Further purification is carried out by chromatography [Tol/Ac (8:2)] over a silica gel column. This gives the title compound (0.84 g) as a colorless solid. TLC, silica gel (glass plates), [toluene/acetone (8:2)], R_f = 0.22.

MS: calc.: $C_{10}H_8O_2S$ (192.2), found: [M^+] 192

A28. 3-[5-(3-Hydroxyprop-1-ynyl)furan-2-yl]prop-2-yn-1-ol

$Pd(Ph_3P)_4$ (580 mg, 3%), CuI (140 mg, 2%) and propargyl alcohol (4.65 ml, 67.7 mmol) are added successively to a solution of 2,5-dibromofuran (5.1 g, 22.6 mmol) in n-propylamine (100 ml), and the mixture is stirred at RT for 1 h and then under reflux for 24 h. More propargyl alcohol (2.0 ml, 33 mmol) is then added and the mixture is stirred under reflux for another 8 h. After cooling, the reaction mixture is filtered off with suction through kieselguhr and washed with ethyl acetate (50 ml). The organic phase is concentrated under reduced pressure. Further purification is carried out by chromatography [Tol/Ac (8:2)] over a silica gel column. This gives the title compound (3.8 g) as a colorless solid. TLC, silica gel (glass plates), [toluene/acetone (8:2)], R_f = 0.40.

MS: calc.: $C_{10}H_8O_3$ (176.2), found: [M^+] 176

A29. Methyl {3-[3-(3-carboxymethoxyprop-1-ynyl)phenyl]prop-2-ynyloxy}acetate

A 60% suspension of NaH (2.1 g, 53.7 mmol) is added to a solution of 3-[3-(3-hydroxyprop-1-ynyl)-phenyl]prop-2-yn-1-ol (A5, 0.5 g, 2.68 mmol) in absolute THF (20 ml), and the mixture is stirred at 70°C for 2 h. After cooling to RT, methyl bromoacetate (5.2 ml, 53.7 mmol) is added dropwise to the reaction solution, and the mixture is stirred at RT overnight. For work-up, the reaction solution is poured into an ice-cooled semisaturated aqueous NH_4Cl solution (25 ml) and extracted (2 ×) with ethyl acetate. The combined organic phases are dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification by chromatography [Tol/Ac (9:1)] over a silica gel column gives the title compound (0.85 g) as a colorless residue. TLC, silica gel, glass plates, [Tol/Ac (7:3)], R_f = 0.80.

A30. {3-[3-(3-Carboxymethoxyprop-1-ynyl)phenyl]prop-2-ynyloxy} acetic acid

An aqueous 1 N NaOH solution (18 ml) is added dropwise to a solution of methyl {3-[3-(3-carboxy-methoxyprop-1-ynyl)phenyl]prop-2-ynyloxy} acetate (A29, 0.85 g, 2.7 mmol) in methanol (50 ml), and the mixture is stirred at RT for 3 h. The pH of the reaction solution is subsequently adjusted to pH 2 using an aqueous 2 N HCl solution. The solution is extracted with ethyl acetate (30 ml, 2 ×) and washed with a saturated NaCl solution (30 ml). The combined organic phases are dried over $MgSO_4$, filtered off and concentrated under reduced pressure. This gives the title compound (0.43 g) as a colorless powder.

A31. Methyl {3-[4-(3-carboxymethoxyprop-1-ynyl)phenyl]prop-2-ynyloxy}acetate

A 60% suspension of NaH (2.1 g, 53.7 mmol) is added to a solution of 3-[4-(3-hydroxyprop-1-ynyl)-phenyl]prop-2-yn-1-ol (A6, 0.5 g, 2.68 mmol) in absolute THF (20 ml), and the mixture is stirred at 70°C for 2 h. After cooling to RT, methyl bromoacetate (5.2 ml, 53.7 mmol) is added dropwise to the reaction solution, and the mixture is stirred at RT overnight. For work-up, the reaction solution is poured into an ice-cooled semisaturated aqueous NH_4Cl solution (25 ml) and extracted (2 ×) with ethyl acetate. The combined organic phases are dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The title compound (0.88 g) is obtained as a colorless powder. TLC, silica gel, glass plates, [Tol/Ac (7:3)], R_f = 0.70.

A32. {3-[4-(3-Carboxymethoxyprop-1-ynyl)phenyl]prop-2-ynyloxy}acetic acid

An aqueous 2 N NaOH solution (10 ml) is added dropwise to a solution of methyl {3-[4-(3-carboxymethoxyprop-1-ynyl)phenyl]prop-2-ynyloxy}acetate (A31; 0.88 g, 2.7 mmol) in methanol (50 ml), and the mixture is stirred at RT for 2 h. The pH of the reaction solution is then adjusted to pH 2 using an aqueous 2 N HCl solution. The solution is extracted with ethyl acetate (30 ml, 2 ×) and washed with a saturated NaCl solution (30 ml). The combined organic phases are dried over $MgSO_4$, filtered off and concentrated under reduced pressure. This gives the title compound (0.75 g) as a colorless powder.

A33. 3-(4-tert-Butyloxycarbonylaminomethylphenyl)propionic acid

4.65 g of methyl 3-(4-aminomethylphenyl)propionate hydrochloride (A34) and 6.17 ml of triethylamine are mixed in 20 ml of dichloromethane. To this mixture, a solution of 4.62 g of di-tert-butyl-dicarbonate in10 ml of dichloromethane is added slowly at 0°C with stirring. Stirring is continued 1 h at 0°C and 3 h at RT. Then the reaction mixture is washed twice with 1N hydrochloric acid solution, with sodium hydrogen carbonate solution and water. After drying over magnesium sulfate, the solvent is removed and the residue (5.6 g) is dissolved in 50 ml of tetrahydrofurane. 13.4 ml of 2N aqueous sodium hydroxide solution is added and the mixture is stirred overnight, neutralized with 6.7 ml of 4N hydrochloric acid solution and the organic solvent is distilled off. The white precipitate is filtered by suction, washed with water and dried to give 4.65 g of the title compound.

MS: calc.: $C_{15}H_{21}NO_4$ (279,3), found: $[MNH_4^+]$ 297,0

A34. Methyl 3-(4-aminomethylphenyl)propionate hydrochloride

5.6 g of methyl 4-(hydroxyimino-methyl)cinnamate (A35) are dissolved in a mixture of 170 ml of methanol and 50 ml of acetic acid and hydrogenated over 0.5 g palladium/carbon (10%) for four hours. The catalyst is filtered off and the solvents are removed. The residue is stirred with ether and then a

solution of hydrogen chloride in ether is added. The white precipitate is filtered by suction, washed with ether and dried in vacuo to give 4.65 g of the title compound.

MS: calc.: $C_{11}H_{15}NO_2$ (193,2), found: $[MH^+]$ 194,0

A35. Methyl 4-(hydroxyimino-methyl)cinnamate

4.0 g of methyl 4-formylcinnamate are dissolved in 40 ml methanol and then 1.6 g hydroxylamine-hydrochloride and 1.9 g sodium acetate are added. The mixture is stirred overnight and then diluted with 300 ml water. The precipitate is filtered by suction, dried in vacuo and crystallized from ethyl acetate/petrolether. This gives 3.56 g of the title compound.

MS: calc.: $C_{11}H_{11}NO_3$ (205,2), found: $[MH^+]$ 206,0

Commercial utility

As tryptase inhibitors, the compounds according to the invention have useful pharmacological properties which make them commercially utilizable. Human tryptase is a serin protease which is the main protein in human mast cells. Tryptase comprises eight closely related enzymes (α1, α2, β1a, β1b, β2, β3, mMCP-7-like-1, mMCP-7-like-2; 85 to 99% sequence identity) (cf. Miller et al., J. Clin. Invest. 84 (1989) 1188-1195; Miller et al., J. Clin. Invest. 86 (1990) 864-870; Vanderslice et al., Proc. Natl. Acad. Sci., USA 87 (1990) 3811-3815; Pallaoro et al., J. Biol. Chem. 274 (1999) 3355-3362). However, only the β-tryptases (Schwartz et al., J. Clin. Invest. 96 (1995) 2702-2710; Sakai et al., J. Clin. Invest. 97 (1996) 988-995) are activated intracellularly and stored in catalytically active form in secretory granules. Compared with other known serin proteases, such as, for example, trypsin or chymotrypsin, tryptase has some special properties (Schwartz et al., Methods Enzymol. 244, (1994), 88-100; G. H. Caughey, „Mast cell proteases in immunology and biology". Marcel Dekker, Inc., New York, 1995). Tryptase from human tissue has a noncovalently-linked tetrameric structure which has to be stabilized by heparin or other proteoglycanes to be proteolytically active. Together with other inflammatory mediators, such as, for example, histamine and proteoglycanes, tryptase is released when human mast cells are activated. Because of this, tryptase is thought to play a role in a number of disorders, in particular in allergic and inflammatory disorders, firstly because of the importance of the mast cells in such disorders and secondly since an increased tryptase concentration was observed in a number of disorders of this type. Thus, tryptase is associated, inter alia, with the following diseases: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of various origins (for example bronchitis, allergic bronchitis, bronchial asthma, COPD); interstitial lung disorders; disorders based on allergic reactions of the upper airways, (pharynx, nose) and the adjacent regions (for example paranasal sinuses, conjunctivae), such as, for example allergic conjunctivitis and allergic rhinitis; disorders of the arthritis type (for example rheumatoid arthritis); autoimmune disorders, such as multiple sclerosis; furthermore periodontitis, anaphylaxis, interstitial cystitis, dermatitis, psoriasis, sclerodermia/systemic sclerosis, inflammatory intestinal disorders (Crohn's disease, inflammatory bowel disease) and others. In particular, tryptase seems to be connected directly to the pathogenesis of asthma (Caughey, Am. J. Respir. Cell Mol. Biol. 16 (1997), 621-628; R. Tanaka, "The role of tryptase in allergic inflammation" in: Protease Inhibitors, IBC Library Series, 1979, Chapter 3.3.1-3.3.23).

A further subject of the invention relates to the compounds according to the invention for use in the treatment and/or prophylaxis of diseases, in particular the diseases mentioned.

The invention likewise relates to the use of the compounds according to the invention for preparing medicaments which are employed for the treatment and/or prophylaxis of the diseases mentioned.

Medicaments for the treatment and/or prophylaxis of the diseases mentioned, which contain one or more of the compounds according to the invention, are furthermore a subject of the invention.

The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical excipients, for example in the form of tablets, coated tablets, capsules, suppositories, patches, emulsions, suspension, gels or solutions, the active compound content advantageously being between 0.1 and 95%.

The person skilled in the art is familiar on the basis of his/her expert knowledge with the excipients which are suitable for the desired pharmaceutical formulations. In addition to solvents, gel-forming agents, ointment bases and other active compound vehicles, it is possible to use, for example, antioxidants, dispersants, emulsifiers, preservatives, solubilizers or permeation promoters.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation. For this purpose, they are either administered directly as a powder (preferably in micronized form) or by nebulization of solutions or suspensions which contain them. With respect to the preparations and administration forms, reference is made, for example, to the details in European Patent 163 965.

For the treatment of dermatoses, the compounds according to the invention are in particular used in the form of those medicaments which are suitable for topical administration. For the preparation of the medicaments, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical excipients and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations which may be mentioned are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The medicaments according to the invention are prepared by processes known per se. The dosage of the active compounds in the case of systemic therapy (p.o. or i.v.) is between 0.1 and 10 mg per kilogram per day.

Biological investigations

The documented pathophysiological effects of mast cell tryptase are caused directly by the enzymatic activity of the protease. Accordingly, they are reduced or blocked by inhibitors which inhibit the enzymatic activity of the tryptase. A suitable measure for the affinity of a reversible inhibitor to the target protease is the equilibrium dissociation constant K_i of the enzyme-inhibitor complex. This K_i value can be determined via the effect of the inhibitor on the tryptase-induced cleavage of a chromogenic peptide-p-nitroanilide substrate or a fluorogenic peptide-aminomethylcoumarin substrate.

Methodology

The dissociation constants for the tryptase-inhibitor complexes are determined under equilibrium conditions in accordance with the general proposals of Bieth (Bieth JG, Pathophysiological Interpretation of kinetic constants of protease inhibitors, Bull. Europ. Physiopath. Resp. 16:183-195, 1980) and the methods of Sommerhoff et al. (Sommerhoff CP et al., A Kazal-type inhibitor of human mast cell tryptase: Isolation from the medical leech Hirudo medicinalis, characterization, and sequence analysis, Biol. Chem. Hoppe-Seyler 375: 685-694, 1994).

Human tryptase is isolated from lung tissue or prepared recombinantly; the specific activity of the protease, determined by titration, is usually greater than 85% of the theoretical value. In the presence of heparin (0.1-50 µg/ml) for stabilizing the protease, constant amounts of the tryptase are incubated with increasing amounts of the inhibitors. After an equilibrium between the reaction partners has formed, the remaining enzyme activity after addition of the peptide-p-nitroanilide substrate tos-Gly-Pro-arg-pNA is determined and the cleavage of the latter is monitored at 405 nm for 3 min. Alternatively, the remaining enzymatic activity can also be determined using fluorogenic substrates. The apparent dissociation constants K_{iapp} (i.e. in the presence of substrate) are subsequently determined by adapting the enzyme rates to the general equation for reversible inhibitors (Morrison JF, Kinetics of the reversible inhibition of enzyme-catalyzed reactions by tight-binding inhibitors, Biochim. Biophys. Acta 185, 269-286, 1969) using non-linear regression:

$$V_i/V_0 = 1 - \{E_t+I_t+K_{iapp}-[(E_t+I_t+K_{iapp})^2-4E_tI_t]^{1/2}\}/2E_t$$

V_i and V_0 are the rates in the presence and absence, respectively, of the inhibitor, and E_t and I_t are the tryptase and inhibitor concentrations, respectively.

The apparent dissociation constants determined for the compounds according to the invention are shown in Table A below, where the numbers of the compounds correspond to the numbers of the compounds in the examples.

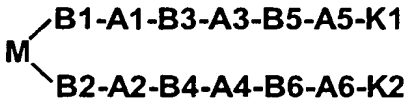
Table A

Inhibition of human tryptase

Compound	K_{iapp} (μM)
1	0.003
2	0.01
3	0.2
4	0.003
5	0.032
6	0.3
7	0.12
8	0.08
9	0.0075
10	0.15
11	0.03
12	0.013
13	0.13
14	0.33
15	0.029

Pat nt Claims

1. Compounds of formula I

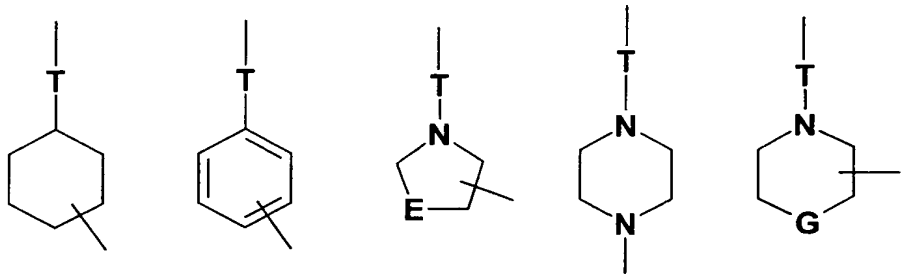


(I)

in which

A1 and A2 are identical or different and are -C(O)-, -NH-, -O- (oxygen), -S- (sulfur), $-S(O)_2-$, $-S(O)_2-NH-$, $-NH-S(O)_2-$, -C(O)-NH-, -NH-C(O)-, -O-C(O)-, -C(O)-O- or a bond,

A3 and A4 are identical or different and are -C(O)-, -O-, -S-, -NH-, -O-C(O)-, -C(O)-O-, -C(O)-NH-, -NH-C(O)- or a bond, or are selected from the group consisting of



where

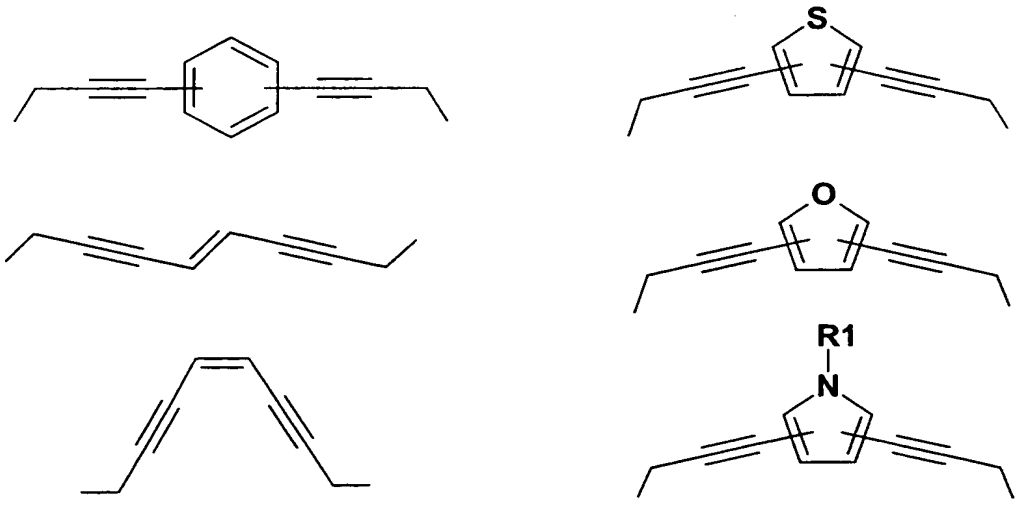
E is -O- (oxygen), -S- (sulfur) or $-CH_2-$ (methylene),

G is -O- (oxygen) or $-CH_2-$ (methylene), and

T is the group -C(O)- or a bond,

A5 and A6 are identical or different and are -C(O)-, -NH-, -O-, -S-, -C(O)-NH-, -NH-C(O)-, -O-C(O)-, -C(O)-O-, -NH-C(O)-NH- or a bond,

M is a central building block selected from the group below



where

R1 is hydrogen, 1-4C-alkyl or 1-4C-alkylcarbonyl,

K1 is -B7-$(C(O))_m$-B9-X1, -B7-$(C(O))_m$-B9-Y1 or -B7-$(C(O))_m$-B9-Z1-B11-X1,

K2 is -B8-$(C(O))_p$-B10-X2, -B8-$(C(O))_p$-B10-Y2 or -B8-$(C(O))_p$-B10-Z2-B12-X2,

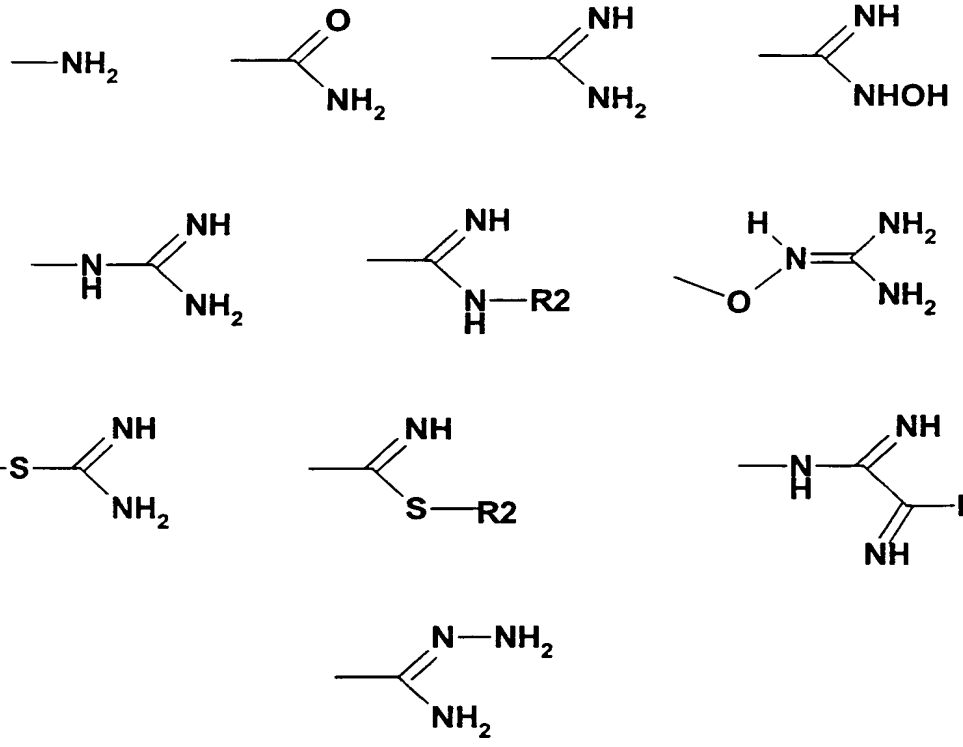
B1, B2, B3, B4, B5 and B6 are identical or different and are a bond or 1-4C-alkylene,

B7, B8, B9, B10, B11 and B12 are identical or different and are a bond or 1-4C-alkylene,

m is 0 or 1,

p is 0 or 1,

X1 and X2 are identical or different and are selected from the group consisting of



where

R2 is 1-4C-alkyl,

Y1 and Y2 are identical or different and are a 4-11C-heteroaryl or 2-7C-heterocycloalkyl radical containing at least one ring nitrogen,

Z1 and Z2 are identical or different and are 5-12C-arylene, 5-12C-heteroarylene, 3-8C-cycloalkylene or 3-8C-heterocycloalkylene,

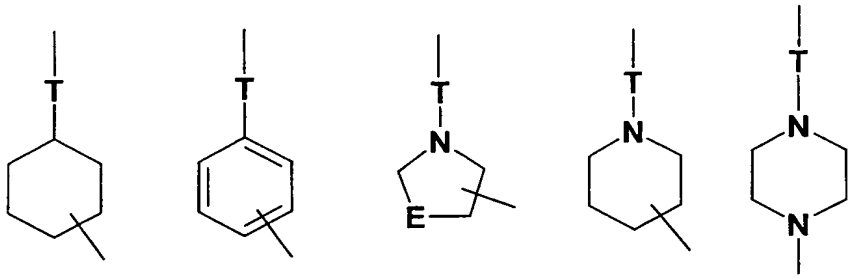
where each arylene, heteroarylene, cycloalkylene, heterocycloalkylene, heteroaryl or heterocycloalkyl may additionally for its part be substituted by one, two or three substituents selected from the group consisting of hydroxyl, halogen, nitro, cyano, amino, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, carboxyl or aminocarbonyl,

and where on the direct route between the terminal nitrogen atoms 20 to 40 bonds have to be present, the salts of these compounds, and the N-oxides of the nitrogen-containing heteroaryls, heterocycloalkyls, heteroarylenes and heterocycloalkylenes, and their salts, where all those compounds are excluded in which one or more of the variables B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, B11 or B12 may assume the meaning of a bond resulting in the direct linkage of two heteroatoms or two carbonyl groups.

2. Compounds of formula I according to claim 1 in which

A1 and A2 are identical or different and are -C(O)-, -NH-, -O-, -C(O)-NH-, -NH-C(O)-, -O-C(O)-, -C(O)-O- or a bond,

A3 and A4 are identical or different and are -C(O)-, -O-, -NH-, -O-C(O)-, -C(O)-O-, -C(O)-NH-, -NH-C(O)- or a bond, or are selected from the group consisting of



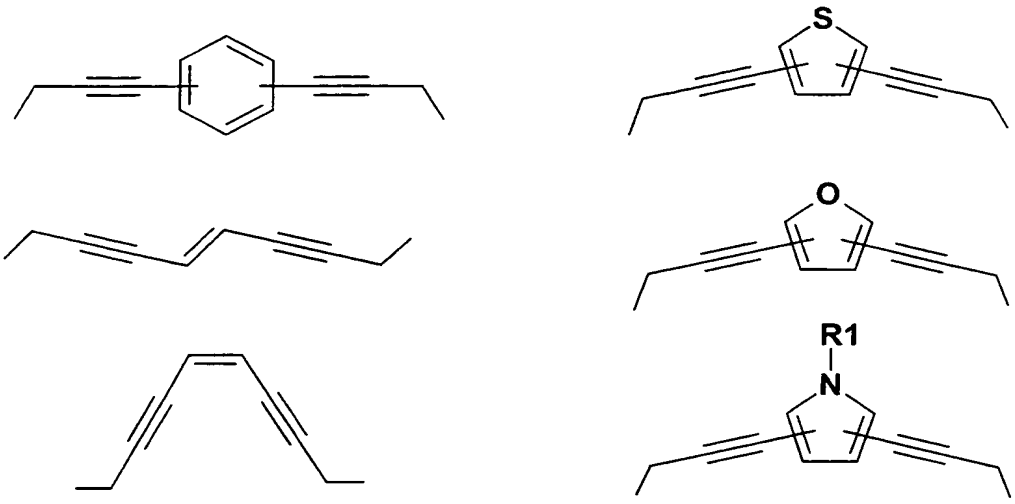
where

E is -O- (oxygen), -S- (sulfur) or -CH_2- (methylene) and

T is the group -C(O)- or a bond,

A5 and A6 are identical or different and are -C(O)-, -NH-, -O-, -C(O)-NH-, -NH-C(O)-, -O-C(O)-, -C(O)-O-, -NH-C(O)-NH- or a bond,

M is a central building block selected from the group below



where

R1 is hydrogen, 1-4C-alkyl or 1-4C-alkylcarbonyl,

K1 is -B7-$(C(O))_m$-B9-X1, -B7-$(C(O))_m$-B9-Y1 or -B7-$(C(O))_m$-B9-Z1-B11-X1,

K2 is -B8-$(C(O))_p$-B10-X2, -B8-$(C(O))_p$-B10-Y2 or -B8-$(C(O))_p$-B10-Z2-B12-X2,

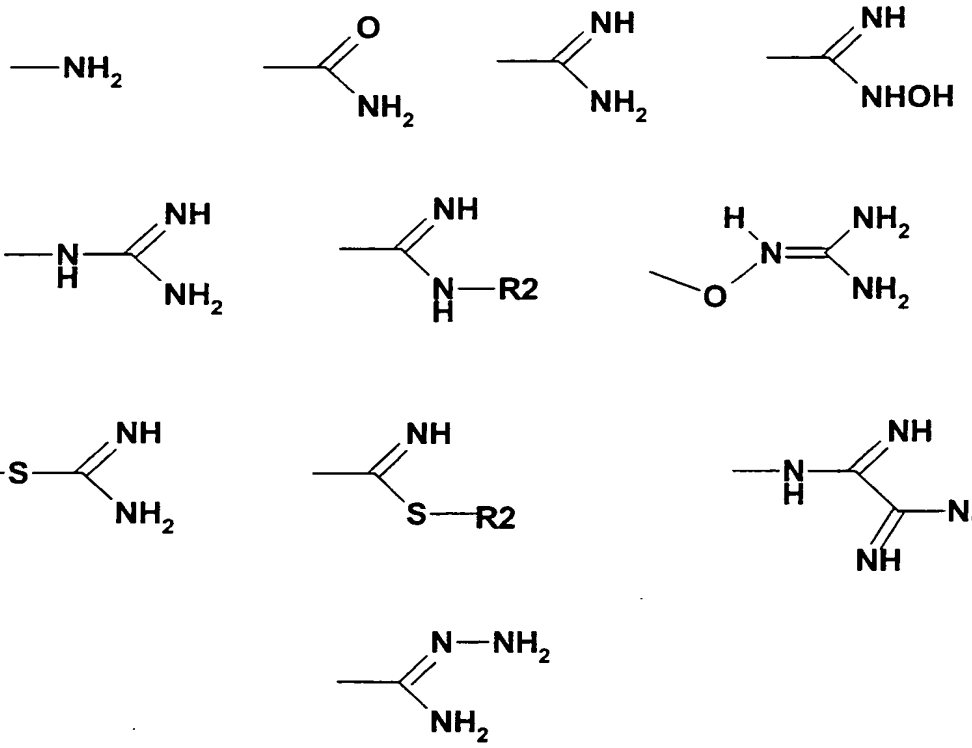
B1, B2, B3, B4, B5 and B6 are identical or different and are a bond or 1-4C-alkylene,

B7, B8, B9, B10, B11 and B12 are identical or different and are a bond or 1-4C-alkylene,

m is 0 or 1,

p is 0 or 1,

X1 and X2 are identical or different and are selected from the group consisting of



where

R2 is 1-4C-alkyl,

Y1 and Y2 are identical or different and are piperid-4-yl, piperid-3-yl, piperazin-1-yl, piperazin-2-yl, morpholin-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, 2-imidazolin-3-yl, 2-imidazolin-2-yl, imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, pyrid-4-yl, pyrid-3-yl, pyridazin-4-yl, pyrimidin-5-yl, pyrimidin-4-yl, indol-3-yl, benzimidazol-4-yl or benzimidazol-5-yl,

Z1 and Z2 are identical or different and are 1,4-phenylene, 1,3-phenylene, 1,4-naphthylene, 2,6-naphthylene, 1,4-cyclohexylene, 1,3-cyclohexylene, 1,3-cyclopentylene, 1,4-piperazinylene, 4,1-piperidinylene, 1,4-piperidinylene, 2,5-pyrrolidinylene, 4,2-imidazolidinylene, 2,5-furylene, 2,5-pyrrolylene, 4,2-pyridylene, 5,2-pyridylene, 2,5-indolylene, 2,6-indolylene, 3,5-indolylene, 3,6-indolylene, 3,5-indazolylene, 3,6-indazolylene, 2,6-quinolinylene, 2,5-benzofuranylene or 4,2-thiazolylene,

where each arylene, heteroarylene, cycloalkylene, heterocycloalkylene, heteroaryl or heterocycloalkyl may additionally for its part be substituted by one, two or three substituents selected from the group consisting of hydroxyl, halogen, nitro, cyano, amino, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyloxy, carboxyl or aminocarbonyl,

and where on the direct route between the terminal nitrogen atoms 20 to 40 bonds have to be present, the salts of these compounds, and the N-oxides of the nitrogen-containing heteroaryls, heterocycloalkyls, heteroarylenes and heterocycloalkylenes, and their salts, where all those compounds are excluded in which one or more of the variables B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, B11 or B12

may assume the meaning of a bond, resulting in the direct linkage of two heteroatoms or carbonyl groups.

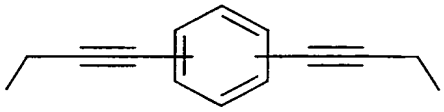
3. Compounds of formula I according to claim 1 in which

A1 and A2 are identical or different and are -O-, -C(O)-, -O-C(O)-, -NH-C(O)- or a bond,

A3 and A4 are identical or different and are 1,4-piperazinylene, 1,4-piperidinylene, 1,4-cyclohexylene, 1,3-phenylene or a bond,

A5 and A6 are identical or different and are -C(O)-, -C(O)-NH-, -NH-C(O)- or -NH-C(O)-NH-,

M is a central building block selected from the group below



K1 is -B7-$(C(O))_m$-B9-Y1 or -B7-$(C(O))_m$-B9-Z1-B11-X1,

K2 is -B8-$(C(O))_p$-B10-Y2 or -B8-$(C(O))_p$-B10-Z2-B12-X2,

B1 and B2 are identical or different and are a bond or methylene,

B3, B4, B5 and B6 are identical or different and are a bond or 1-3C-alkylene,

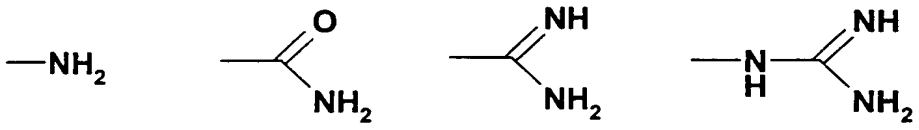
B7, B8, B9 and B10 are identical or different and are a bond or 1-4C-alkylene,

B11 and B12 are identical or different and are a bond or methylene,

m is 0,

p is 0,

X1 and X2 are identical or different and are selected from the groups below



Y1 and Y2 are imidazol-1-yl,

Z1 and Z2 are identical or different and are 5,2-pyridinylene, 6-methyl-5,2-pyridinylene, 4,1-piperidinylene, 3,6-indazolylene, 3,6-indolylene, 1,3-phenylene, 1,4-phenylene, 1,3-cyclohexylene or 1,4-cyclohexylene,

and where on the direct route between the terminal nitrogen atoms 20 to 40 bonds have to be present, the salts of these compounds, and also the N-oxides of the nitrogen-containing heteroaryls, heteroarylenes and heterocycloalkylenes, and their salts, where all those compounds are excluded in which one or more of the variables B1, B2, B3, B4, B5, B6, B7, B8, B9, B10, B11 or B12 may assume the meaning of a bond, resulting in the direct linkage of two heteroatoms or carbonyl groups.

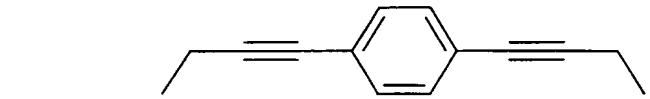
4. Compounds of formula I according to claim 1 in which

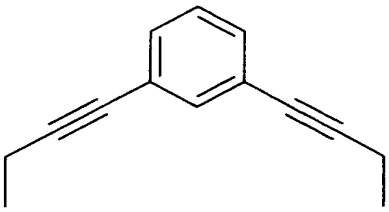
A1 and A2 are -O-C(O)-,

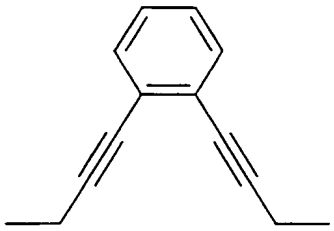
A3 and A4 are 1,4-piperazinylene,

A5 and A6 are identical or different and are -C(O)- or -C(O)-NH-,

M is a central building block selected from the groups below







K1 is -B7-$(C(O))_m$-B9-Z1-B11-X1,

K2 is -B8-$(C(O))_p$-B10-Z2-B12-X2,

B1, B2, B3, B4, B5 and B6 are a bond,

B7 and B8 are identical or different and are a bond or methylene,

B9 and B10 are a bond,

B11 and B12 are methylene,

m is 0,

p is 0,

X1 and X2 are amino,

Z1 and Z2 are identical or different and are 1,4-phenylene or 1,4-cyclohexylene,

and the salts of these compounds.

5. Compounds of formula I according to claim 1 with the chemical name

1,2-bis[4-(trans-4-aminomethylcyclohexylcarbonyl)-1-piperazinylcarbonyl-1-oxyprop-2-ynyl]benzene;

1,4-bis[4-(trans-4-aminomethylcyclohexylcarbonyl)-1-piperazinylcarbonyl-1-oxyprop-2-ynyl]benzene;

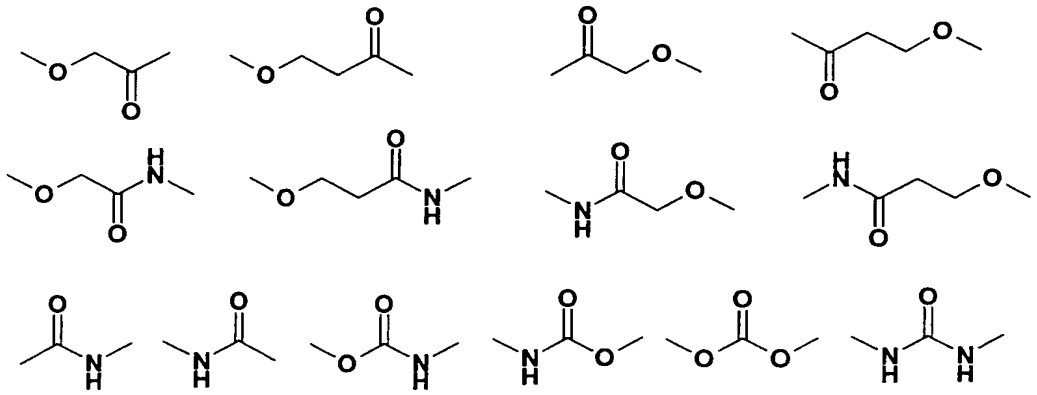
1,2-bis[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyprop-2-ynyl]benzene;

1,3-bis[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyprop-2-ynyl]benzene;

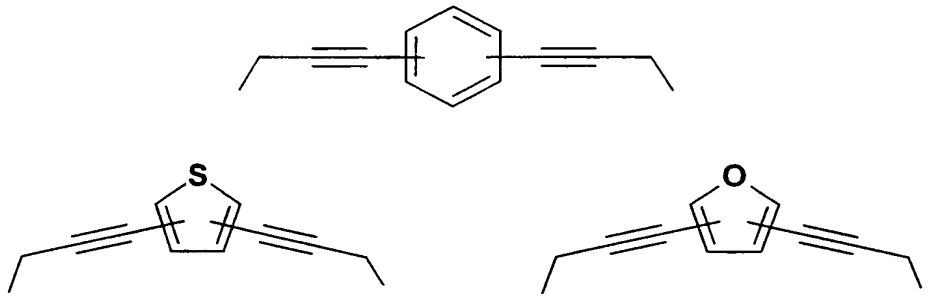
and the salts of these compounds.

6. Compounds of formula I according to claim 1 in which

-B1-A1-B3-A3-B5-A5- and -B2-A2-B4-A4-B6-A6- are identical or different and are selected from the groups below



M is a central building block selected from the groups below



K1 is -B7-$(C(O))_m$-B9-Y1 or -B7-$(C(O))_m$-B9-Z1-B11-X1,

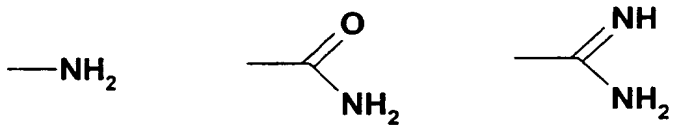
K2 is -B8-$(C(O))_p$-B10-Y2 or -B8-$(C(O))_p$-B10-Z2-B12-X2,

B7, B8, B9, B10, B11 and B12 are identical or different and are a bond or 1-2C-alkylene,

m is 0,

p is 0,

X1 and X2 are identical or different and are selected from the groups below



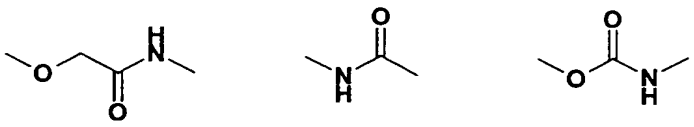
Y1 and Y2 imidazol-1-yl,

Z1 and Z2 are identical or different and are 5,2-pyridinylene, 6-methyl-5,2-pyridinylene, 4,1-piperidinylene, 3,6-indazolylene, 3,6-indolylene, 1,3-phenylene, 1,4-phenylene, 1,3-cyclohexylene or 1,4-cyclohexylene,

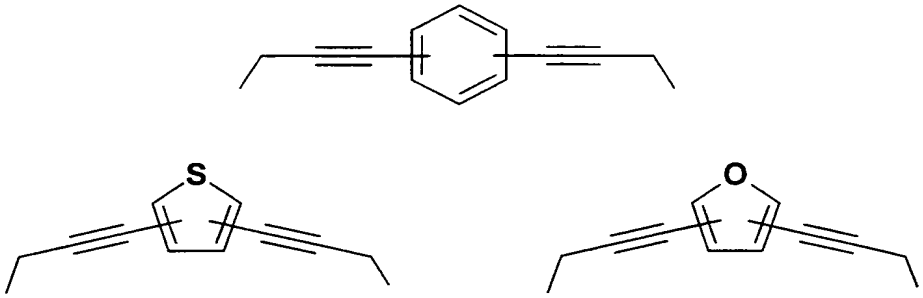
and where on the direct route between the terminal nitrogen atoms 20 to 33 bonds have to be present, the salts of these compounds, and also the N-oxides of the nitrogen-containing heteroaryls, heteroarylenes and heterocycloalkylenes, and their salts.

7. Compounds of formula I according to claim 1 in which

-B1-A1-B3-A3-B5-A5- and -B2-A2-B4-A4-B6-A6- are identical or different and are selected from



M is a central building block selected from the group below



K1 is -B7-$(C(O))_m$-B9-Z1-B11-X1,

K2 is -B8-$(C(O))_p$-B10-Z2-B12-X2,

B7 and B8 are identical or different and are a bond or methylene,

B9 and B10 are a bond,

B11 and B12 are methylene,

m is 0,

p is 0,

X1 and X2 are amino,

Z1 and Z2 are identical or different and are 1,4-phenylene or 1,3-phenylene,

and the salts of these compounds.

8. Compounds of formula I according to claim 1 with the chemical name

1,3-Bis-(4-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-benzene;

1,2-Bis-(4-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-benzene;

3,4-Bis-(4-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-thiophene;

2,5-Bis-(4-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-furan;

2,5-Bis-(3-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-furan;

3,4-Bis-(3-aminomethylbenzylaminocarbonyl-1-oxyprop-2-ynyl)-thiophene;

1,4-Bis-(4-aminomethylbenzylaminocarbonylmethyl-1-oxyprop-2-ynyl)-benzene;

1,3-Bis-(4-aminomethylbenzylaminocarbonylmethyl-1-oxyprop-2-ynyl)-benzene;

1,4-Bis-(4-aminomethylbenzylcarbonyl-1-aminoprop-2-ynyl)-benzene;

1,2-Bis-(4-aminomethylbenzylcarbonyl-1-aminoprop-2-ynyl)-benzene;

1,4-Bis-(4-aminomethylphenylethylcarbonyl-1-aminoprop-2-ynyl)-benzene;

and the salts of these compounds.

9. A medicament comprising one or more compounds of formula I according to claim 1 together with customary pharmaceutical auxiliaries and/or excipients.

10. Use of compounds of formula I according to claim 1 for the production of medicaments for the treatment of airway disorders.